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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 315/00

A2

(11) International Publication Number: WO 99/47497

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/CA99/00212

(22) International Filing Date: 12 March 1999 (12.03.99)

(30) Priority Data:

60/077,990	13 March 1998 (13.03.98)	US
9815856.1	21 July 1998 (21.07.98)	GB

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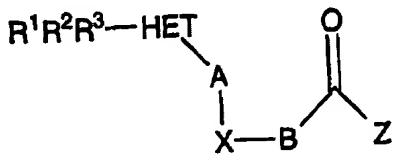
(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(I)

(57) Abstract

Compounds of formula (I), as well as pharmaceutically acceptable salts, hydrates and esters thereof, are disclosed. The compounds are useful for treating or preventing prostaglandin mediated diseases. Pharmaceutical compositions containing such compounds and methods of treatment are also included.

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CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

BACKGROUND OF THE INVENTION

The present invention relates to compounds which are useful for treating or preventing prostaglandin mediated diseases, methods of treatment and pharmaceutical compositions containing such compounds. The compounds are structurally different from conventional NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.

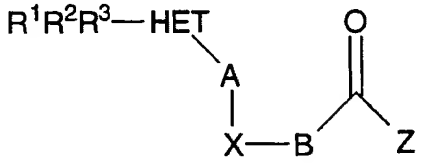
Two review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids: From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87. An article from *The British Journal of Pharmacology* (1994, 112, 735-740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord.

Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties, and in addition inhibit hormone-induced uterine contractions. Moreover, the compounds have anti-cancer effects.

The compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:



I

as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$- or $-CR^7=CR^7$- , wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}$- ;

B represents - $(C(R^{18})2)_p$-Y- $(C(R^{18})2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}$- , p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, - $(C(R^4)2)_pSR^5$, $-(C(R^4)_2)_pOR^8$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, - CO_2R^9, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl,

or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})_{0-2}$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})_{0-3}$, $CH_2Ph(R^{11})_{0-3}$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R^{15} are independently lower alkyl, halogen, CF_3, OR^{16}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3, $HET(R^a)_{4-9}$, lower alkyl-$HET(R^a)_{4-9}$ or lower alkenyl-$HET(R^a)_{4-9}$;

each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3 or $Ph(R^{13})_2$

and

each R^a is independently selected from the group consisting of:

H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

Pharmaceutical compositions are also included which are comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

A method of treating or preventing a prostaglandin mediated disease is also included which is comprised of administering to a mammalian patient in need thereof, a compound of formula I in an amount which is effective for treating or preventing a prostaglandin mediated disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to carboxylic acids and acylsulfonamides, which are ligands at prostaglandin receptors, as well as a method for treating or preventing a prostaglandin mediated disease comprising administering to a patient in need of such a treatment of an amount of compound of Formula I which is effective for treating or preventing a prostaglandin mediated disease.

The invention described in this patent application is described using the following definitions unless otherwise indicated.

HET represents a 5-12 membered aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and N wherein n is 0, 1 or 2. HET may be substituted with up to three substituents on the aromatic ring system, R^1, R^2 and R^3. "Aromatic ring systems" as used herein includes aryl and heteroaryl groups such as benzene, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, triazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, 1,2-methylenedioxybenzene and pyrrole.

HET^2 is a subset of HET and represents a member selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl.

Aryl refers to aromatic 6-10 membered groups having 1-2 rings and alternating (resonating) double bonds. Examples include phenyl, biphenyl and naphthyl.

Heteroaryl refers to aromatic 5-12 membered groups having alternating (resonating) double bonds and containing from 1-4 heteroatoms selected from O, $S(O)_n$ and N. Examples include the following: : quinoline, furan, benzofuran, thiophene, benzothiophene, thiazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, oxazole, indole, isoindole, pyridine, isoquinoline, imidazole, thiazole, triazole, 1,3-methylene dioxobenzene, pyrrole and naphthyridine,

Heterocyclyl refers to non-aromatic 5-12 membered cyclic groups having 1-4 heteroatoms selected from O, $S(O)_n$ and N. Examples of heterocyclic groups are piperidine, piperazine, pyrrolidine, tetrahydrofuran, tetrahydropyran and morpholine.

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group X in positions which are ortho relative to each other. Examples are selected from the group consisting of: phenyl, naphthyl, biphenyl, quinoline, furan, benzofuran, pyridyl, pyrrole, thiophene, benzothiophene, thiazole, benzothiazole, 1,2,5-

thiadiazole, triazole, 1,2-methylenedioxybenzene, thienopyridine, oxazole and indole.

The terms alkyl, alkenyl, and alkynyl mean linear, branched, and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, s- and t-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, and the like. When propyl and butyl are recited without the isomeric form being specified, these include all isomers thereof.

"Lower alkenyl" means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, cyclopropen-1-yl, cyclohexen-3-yl and the like. When cis or trans is not specified, both are intended in pure form as well as in the form of a mixture of isomers.

"Lower alkynyl" means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, 2-(cyclopropyl)ethenyl, 3-(cyclobutyl)-1-propynyl and the like.

Halogen (halo) includes F, Cl, Br and I.

The following abbreviations have the indicated meanings:

AIBN	=	2.2'-azobisisobutyronitrile
B.P.	=	benzoyl peroxide
Bn	=	benzyl
CCl_4	=	carbon tetrachloride
D	=	$-O(CH_2)_3O-$
DAST	=	diethylamine sulfur trifluoride
DCC	=	dicyclohexyl carbodiimide
DCI	=	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
DEAD	=	diethyl azodicarboxylate
DIBAL	=	diisobutyl aluminum hydride
DME	=	ethylene glycol dimethylether
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et_3N	=	triethylamine
LDA	=	lithium diisopropylamide

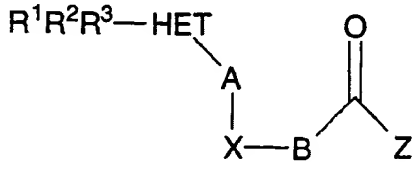
	m-CPBA	=	metachloroperbenzoic acid
	NBS	=	N-bromosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
	Ph	=	phenyl
	1,2-Ph	=	1,2-benzenediyl
	Pyr	=	pyridinediyl
	Qn	=	7-chloroquinolin-2-yl
	Rs	=	$-CH_2SCH_2CH_2Ph$
	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
	THP	=	tetrahydropyran-2-yl

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

It is intended that the definition of any substituent (e.g., R^5, R^6, etc.) in a particular molecule be independent of its definition elsewhere in the molecule. Thus, $-N(R^6)_2$ represents -NHH, $-NHCH_3$, $-NHC_6H_5$, and the like.

In one aspect of the invention, the invention relates to a compound represented by formula I:



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as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$ or CR^7=CR^7, wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or -CR^{18} = CR^{18}- ;

B represents - $(C(R^{18})_2)_p$-Y- $(C(R^{18})_2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or -CR^{18} = CR^{18}- , p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, -$(C(R^4)2)_pSR5$, $-(C(R^4)_2)_pOR^8$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, -CO_2R^9, $-CON(R^6)_2$ or

$-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl,

or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})_{0-2}$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms,

optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})_{0-3}$, $CH_2Ph(R^{11})_{0-3}$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R^{15} are independently lower alkyl, halogen, CF_3, OR^{16}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3 , $HET(R^a)_{4-9}$, lower alkyl-$HET(R^a)_{4-9}$ or lower alkenyl-$HET(R^a)_{4-9}$;

each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3 or $Ph(R^{13})_2$

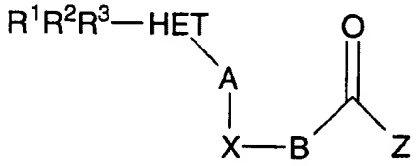
and

each R^a is independently selected from the group consisting of: H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl,

C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, C(O) C_{2-6}alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, and CO_2C_{2-6}alkynyl,

said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

In another embodiment of the invention, the invention relates to compounds represented by formula I:



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as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , - $C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$ or CR^7=CR^7, wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}-$;

B represents $-(C(R^{18})_2)_p$-Y- $(C(R^{18})_2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}-$, p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, $-(C(R^4)2)_pSR5$, $-(C(R^4)_2)_pOR^6$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, $-CO_2R^9$, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl, or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})0-2$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})0-3$, $CH_2Ph(R^{11})0-3$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R15 are independently lower alkyl, halogen, CF_3, OR^{16}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn, CHF_2 or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3 , $HET^2(R^a)_{4-9}$, lower alkyl-$HET^2(R^a)_{4-9}$ or lower alkenyl-$HET^2(R^a)_{4-9}$, wherein HET^2 represents a member selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl;

each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 , CF_3 or $Ph(R^{13})_2$

and

each R^a is independently selected from the group consisting of:

H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, C(O) C_{2-6}alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, and CO_2C_{2-6}alkynyl,

said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

An embodiment of the present invention which is of particular interest is represented by formula I wherein HET represents a member selected from the group consisting of: benzene, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran,

thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, triazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, 1,2-methylenedioxybenzene and pyrrole.

More particularly, an embodiment of the present invention is represented by formula I wherein HET is selected from the group consisting of: benzene, biphenyl, naphthylene, indole, thiophene, benzofuran and quinoline. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein A represents a one or two atom moiety and is selected from the group consisting of: S, S(O), SO_2, CH_2, -C(O)- , -OCH_2-, -CHOH- , -C(OH)(CH_3)- and -CH_2-O- . More particularly, A is selected from the group consisting of: : S, S(O), SO_2, CH_2, -C(O)-. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein X represents phenyl optionally substituted with R^{14} and R^{15}. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I. More particularly, X represents phenyl and R^{14} and R^{15} are absent or represent halo. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein B is CH=CH or 1,2-cyclopropyl, and in particular, where B is CH=CH in the E-isomeric form. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein Z is $NHSO_2R^{19}$. Within this subset of compounds of the invention, all other variables are as originally described with respect to formula I.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein Z is $NHSO_2R^{19}$ and R^{19} represents a member selected from the group consisting of: lower alkyl and $HET(R^a)_3$. Within this aspect of the invention, HET is selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein Z is $NHSO_2R^{19}$ and R^{19} represents benzene or thiophene, substituted with $R^1R^2R^3$.

Another embodiment of the present invention that is of particular interest is represented by formula I wherein Z represents OH. Within this subset, all other variables are as originally defined.

A subset of compounds that is of particular interest is defined with respect to formula I wherein:

HET represents a member selected from the group consisting of: phenyl, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole and pyrrole;

A represents a one or two atom moiety and is selected from the group consisting of: S, S(O), SO_2, CH_2, -C(O)- , $-OCH_2-$, -CHOH- , -C(OH)(CH_3)- and $-CH_2-O-$;

X represents phenyl optionally substituted with R^{14} and R^{15} ;

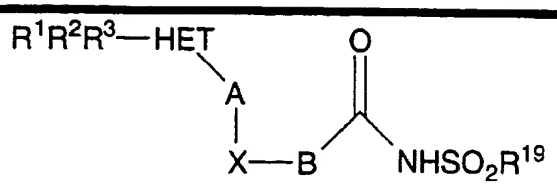
B is CH=CH;

Z is $NHSO_2R^{19}$ and

R^{19} represents a member selected from the group consisting of: lower alkyl and $HET(R^a)_3$.

Examples of compounds of the present invention are shown in Tables I and II below.

Table I



Ia

(Compounds 1-323 and 347-454)

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
1-naphthyl	CH_2	1,2-Ph	CH=CH	$Ph(F)_5$	1
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	$Ph(F)_5$	2
3-methylindol -1-yl	CH_2	1,2-Ph	CH=CH	2-thienyl	3
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	4
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	phenyl	5
3-methylindol -1-yl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	6
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	7
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	8
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	9
2,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	10
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	$Ph(F)_5$	11
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	12
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-thienyl	13
3,4-chloro fluoro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	14
1-naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	15
3,4-dichloro phenyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	16
4-methylthio phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	17
4-chlorophenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	18
2-naphthyl	S	1,2-Ph	CH=CH	2-thienyl	19
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	2-thienyl	20
2-naphthyl	S(O)	1,2-Ph	CH=CH	2-thienyl	21
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	phenyl	22
2-benzofuranyl	CH_2	1,2-Ph	CH=CH	2-thienyl	23

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3,5-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	24
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	25
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	26
3-(1,2-(methylene dioxy)benzene)	CH_2	1,2-Ph	CH=CH	2-thienyl	27
2-naphthyl	O	1,2-Ph	CH=CH	2-thienyl	28
Rs-2-phenyl	CH_2	1,2-Ph	CH_2-O	2-thienyl	29
Rs-2-phenyl	CH_2	1,2-Ph	CH_2-CH_2	2-thienyl	30
2-naphthyl	$S(O)_2$	1,2-Ph	CH_2-O	2-thienyl	31
3-((2-(Qn)vinyl)) phenyl	CH_2	1,2-Ph	CH_2-O	2-thienyl	32
2-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	33
3-((2-(Qn)vinyl)) phenyl	SO	1,2-Ph	CH_2-O	2-thienyl	34
3-((2-(Qn)vinyl)) phenyl	-CHOH-	1,2-Ph	CH_2-O	2-thienyl	35
3-((2-(Qn)vinyl)) phenyl	$S(O)_2$	1,2-Ph	CH_2-O	phenyl	36
3-((2-(Qn)vinyl)) phenyl	O-CH_2	1,2-Ph	CH_2-O	2-thienyl	37
3-tolyl-D-3-phenyl	O-CH_2	1,2-Ph	CH_2-O	2-thienyl	38
3-((2-(Qn)vinyl)) phenyl	CH(OH)-CH_3-	1,2-Ph	CH_2-O	phenyl	39
3-((2-(Qn)vinyl)) phenyl	S	1,2-Ph	CH_2-O	2-thienyl	40
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	CH_2-O	phenyl	41
3-((2-(Qn)vinyl)) phenyl	C=O	1,2-Ph	CH_2-O	2-thienyl	42
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	$C(CH_3)_2$-O	2-thienyl	43
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	CH_2-O	2-thienyl	44
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	45
2-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	46
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	47
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-fluoro phenyl	48

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-chloro phenyl	49
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-propyl phenyl	50
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dichloro thienyl	51
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	styryl	52
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	53
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	54
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-bromo phenyl	55
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	56
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	57
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	58
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	59
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-butyl-phenyl	60
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	butyl	61
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	62
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	63
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	64
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	65
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	66
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	67
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	68
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	69
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	70
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	71

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro-methyl)-hydroxy methyl)phenyl	72
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	73
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	74
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	75
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	cyclohexyl	76
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	cyclopentyl	77
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-morpholinyl	78
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-naphthyl	79
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	80
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	81
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-furanyl	82
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	83
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	84
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	85
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-indolyl	86
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	87
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	88
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	89
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	90
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	91
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	92
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	93
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	94
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	95
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	96
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	97

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-butyl-phenyl	98
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3) phenyl	99
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)-hydroxy methyl)phenyl	100
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-bromophenyl	101
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	102
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	103
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	104
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	105
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	106
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	107
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	108
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	109
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-fluorophenyl	110
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	cyclohexyl	111
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	cyclopentyl	112
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-morpholinyl	113
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	butyl	114
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-chlorophenyl	115
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-propylphenyl	116
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-naphthyl	117
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-thiazolyl	118
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	1-imidazolyl	119
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	120
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	121
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	122
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-furanyl	123
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	124
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-pyridinyl	125

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-styryl	126
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-difluoro-phenyl	127
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-dichloro-phenyl	128
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	129
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-indolyl	130
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-nitrophenyl	131
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-cyanophenyl	132
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	133
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3)-phenyl	134
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	135
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	136
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	137
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-fluorophenyl	138
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-chlorophenyl	139
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-propylphenyl	140
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	141
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-styryl	142
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluoro phenyl	143
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	144
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-bromophenyl	145
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	146
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	147
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	148
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	149

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-butylphenyl	150
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	n-butyl	151
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	152
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	153
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	154
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	155
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	156
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	157
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	158
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	159
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	160
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	161
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)hydroxy methyl)phenyl	162
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	163
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	164
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	165
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	cyclohexyl	166
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	cyclopentyl	167
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-morpholinyl	168
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-naphthyl	169

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	170
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	171
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-furanyl	172
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	173
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	174
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	175
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-indolyl	176
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	177
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	178
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3) phenyl	179
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	180
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	181
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	182
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-fluorophenyl	183
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-chlorophenyl	184
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-propylphenyl	185
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	186
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-styryl	187
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	188
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	189
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-bromo phenyl	190
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	191

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	192
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	193
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	194
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-butylphenyl	195
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	n-butyl	196
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	197
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-trifluoromethyl phenyl	198
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	199
1-(3-methyl) indolyl	SO_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	200
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	201
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	202
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	203
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	204
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	205
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	206
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)hydroxy methyl)phenyl	207
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	208
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl)ethyl)-phenyl	209
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	210
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	cyclohexyl	211

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	cyclopentyl	212
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-morpholinyl	213
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-naphthyl	214
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	215
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	216
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-furanyl	217
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	218
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	219
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	220
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-indolyl	221
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	222
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	223
2-naphthyl	CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	224
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-isopropyl phenyl	225
2-naphthyl	CH_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	226
2-naphthyl	CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	227
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-chlorophenyl	228
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-fluorophenyl	229
2-naphthyl	CH_2	1,2-Ph	CH=CH	2,5-dichloro-3-thienyl	230
2-naphthyl	CH_2	1,2-Ph	CH=CH	3-chloro-4-fluoro phenyl	231
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-methoxy phenyl	232
2-naphthyl	CH_2	1,2-Ph	CH=CH	butyl	233
2-naphthyl	CH_2	1,2-Ph	CH=CH	3-trifluoro methylphenyl	234

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-((1-hydroxy-1-methyl)ethyl) phenyl	235
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-(methyl sufonyl)phenyl	236
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-(benzyloxy) phenyl	237
2-naphthyl	CH_2	1,2-Ph	CH=CH	cyclohexyl	238
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-morpholinyl	239
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-thiazolyl	240
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-furanyl	241
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-pyridinyl	242
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-cyanophenyl	243
2-naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	244
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-isopropyl phenyl	245
2-naphthyl	SO_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	246
2-naphthyl	SO_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	247
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-chlorophenyl	248
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-fluorophenyl	249
2-naphthyl	SO_2	1,2-Ph	CH=CH	2,5-dichloro-3-thienyl	250
2-naphthyl	SO_2	1,2-Ph	CH=CH	3-chloro-4-fluorophenyl	251
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-methoxy phenyl	252
2-naphthyl	SO_2	1,2-Ph	CH=CH	butyl	253
2-naphthyl	SO_2	1,2-Ph	CH=CH	3-trifluoro methylphenyl	254
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-((1-hydroxy-1-methyl)ethyl) phenyl	255
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-(methyl sufonyl)phenyl	256
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-(benzyloxy) phenyl	257
2-naphthyl	SO_2	1,2-Ph	CH=CH	cyclohexyl	258
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-morpholinyl	259
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-thiazolyl	260
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-furanyl	261
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-pyridinyl	262

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-cyanophenyl	263
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	264
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	4-isopropyl phenyl	265
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	2,3-dichloro phenyl	266
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	3,4-difluoro phenyl	267
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	268
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	4-isopropyl phenyl	269
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	270
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	271
2-naphthyl	S	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	272
2-naphthyl	S	1,2-Ph	CH=CH	4-isopropyl phenyl	273
2-naphthyl	S	1,2-Ph	CH=CH	2,3-dichloro phenyl	274
2-naphthyl	S	1,2-Ph	CH=CH	3,4-difluoro phenyl	275
2-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	276
2-(6-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-thienyl	277
2-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	2-thienyl	278
2-(6-benzyloxy) naphthyl	S	1,2-Ph	1,2-c-propyl	2-thienyl	279
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	280
2-(5-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-thienyl	281
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	2-thienyl	282
2-(5-benzyloxy) naphthyl	S	1,2-Ph	1,2-c-propyl	2-thienyl	283
2-(6-(4-trifluoro methyl)benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	284

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(6-(4-trifluoro methyl)benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	285
2-(6-(4-trifluoro methyl)benzyl oxy))naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	286
2-(6-(4-trifluoro methyl)benzyl oxy))naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	287
1-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	288
1-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	289
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	290
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	291
2-(6-(4-fluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	292
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	293
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	294
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	295
2-(6-(4-fluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	296
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	297
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	298
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	299
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	300
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	301

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	302
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	303
2-naphthyl	SO	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	304
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	305
2-naphthyl	O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	306
2-(5-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	307
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	308
2-(5-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	309
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	310
1,2-Ph	SO_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	311
2-naphthyl	S	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	312
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	313
2-naphthyl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	314
3-methyl indol-1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	315
3-methyl indol-1-yl	S	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	316
3-methyl indol-1-yl	CH_2-O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	317
3-methyl indol-1-yl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	318
3-methyl indol-1-yl	O-CH_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	319
3-methyl indol-1-yl	SO	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	320
3-methyl indol-1-yl	CH_2-O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	321
3-methyl indol-1-yl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	322
3-methyl indol-1-yl	SO_2	4-Cl-1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	323

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	347
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	348
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	349
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	350
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	351
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	352
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	353
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	354
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	355
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	356
2-naphthyl	CH_2	4,5-Cl_2-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	357
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	358
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	359
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	360
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	361
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	362
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	363
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	364
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	365

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-trifluoro methoxy-5-chlorophenyl	366
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	367
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	368
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	369
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	370
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	371
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	372
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	373
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	374
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	375
2-(6-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	376
2-(6-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	377
2-(6-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	378
2-(6-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	379
2-(6-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	380
2-(6-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	381
2-(7-chloro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	382
2-(7-chloro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	383
2-(7-chloro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	384
2-(7-chloro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	385
2-(7-chloro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	386

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(7-chloro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	387
2-(7-chloro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	388
2-(6,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	389
2-(6,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	390
2-(6,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	391
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	392
2-(6,7-difluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	393
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	394
2-(6,7-difluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	395
2-(6,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	396
2-(6,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	397
2-(6,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	398
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	399
2-(6,7-difluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	400
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	401
2-(6,7-difluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	402
2-(5,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	403
2-(5,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	404
2-(5,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	405
2-(5,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	406
2-(6-fluoro) quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	407
2-(6-fluoro) quinolinyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	408

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(6-fluoro) quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	409
2-(6-fluoro) quinolinyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	410
2-(6-fluoro) quinolinyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	411
2-(6-fluoro) quinolinyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	412
2-(5,7-difluoro)-quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	413
2-(5,7-difluoro)-quinolinyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	414
2-(5,7-difluoro)-quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	415
2-(5,7-difluoro)-quinolinyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	416
2-(5,7-difluoro)-quinolinyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	417
2-(5,7-difluoro)-quinolinyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	418
3,4-dichloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	419
3,4-dichloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	420
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	421
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	422
3,4-dichloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	423
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	424
3,4-dichloro phenyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	425
4-chloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	426
4-chloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	427
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	428
4-chloro phenyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	429
4-chloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	430

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	431
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	432
3,4-dichloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	433
3,4-dichloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	434
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	435
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	436
3,4-dichloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	437
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	438
3,4-dichloro phenyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-thienyl	439
4-chloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	440
4-chloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	441
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	442
4-chloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	443
1-(5-chloro) indolyl	CH_2	3,2-Pyr	CH=CH	2,4-(Me)2-thiazol-5-yl	444
1-(5-chloro) indolyl	CH_2	3,2-Pyr	CH=CH	2-thienyl	445
1-(6-(4-chloro) phenyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	3-chloro-4-fluorophenyl	446
2-(6-difluoro methoxy) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	447
2-naphthyl	CH_2	4-MeO-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	448
2-naphthyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	449
2-(6-chloro naphthyl)	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	450
1-(5-phenyl methoxy) indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	451

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(benzo[b] thiophenyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	452
5-(1-benzyl) indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	453
1-(6-(4-chloro) phenyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	454

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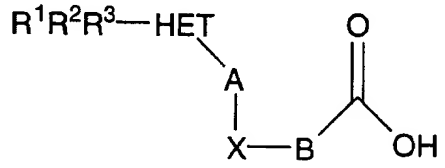
Table II



I-b

(Compounds 324-346 and 455-542)

$R^1R^2R^3$-Het	A	X	B	Cpd
2-naphthyl	$S(O)_2$	1,2-phenyl	CH=CH	324
2-naphthyl	S	1,2-phenyl	CH=CH	325
4-methylthiophenyl	CH_2	1,2-phenyl	CH=CH	326
3-methylindol-1-yl	CH_2	1,2-phenyl	CH=CH	327
3-chloro-4-fluorophenyl	CH_2	1,2-phenyl	CH=CH	328
4-chlorophenyl	CH_2	1,2-phenyl	CH=CH	329
2-naphthyl	CH_2	1,2-phenyl	CH=CH	330
2-naphthyl	$S(O)_2$	1,2-phenyl	1,2-c-propyl	331
2-naphthyl	$S(O)_2$	1,2-phenyl	CH_2-CH_2	332
2-naphthyl	S	1,2-phenyl	CH=CH	333
3,4-dichlorophenyl	$S(O)_2$	1,2-phenyl	CH_2-CH_2	334
3,4-dichlorophenyl	CH_2	1,2-phenyl	CH=CH	335
2-(6-benzyloxy)naphthyl	CH_2	1,2-phenyl	CH=CH	336
2-(6-benzyloxy)naphthyl	CH_2	1,2-phenyl	1,2-c-propyl	337
2-(6-benzyloxy)naphthyl	SO_2	1,2-phenyl	1,2-c-propyl	338
2-(6-benzyloxy)naphthyl	CH_2-O	1,2-phenyl	1,2-c-propyl	339
2-(6-benzyloxy)naphthyl	O-CH_2	1,2-phenyl	1,2-c-propyl	340
2-(6-benzyloxy)naphthyl	SO_2	1,2-phenyl	CH=CH	341
2-(6-benzyloxy)naphthyl	CH_2-O	1,2-phenyl	CH=CH	342

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(6-benzyloxy)naphthyl	O-CH_2	1,2-phenyl	CH=CH	343
2-(6-benzyloxy)naphthyl	S	1,2-phenyl	CH=CH	344
2-(7-benzyloxy)naphthyl	SO_2	1,2-phenyl	CH=CH	345
2-(6-(4-trifluoromethyl) benzyloxy))naphthyl	CH_2	1,2-phenyl	CH=CH	346
2-(6-fluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	455
2-(6-fluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	456
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	457
2-(6-fluoro)naphthyl	CH_2	1,2-Ph	CH=CH	458
2-(6-fluoro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	459
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	460
2-(7-fluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	461
2-(7-fluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	462
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	463
2-(7-fluoro)naphthyl	CH_2	1,2--Ph	CH=CH	464
2-(7-fluoro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	465
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	466
2-(6-chloro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	467
2-(6-chloro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	468
2-(6-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	469
2-(6-chloro)naphthyl	CH_2	1,2-Ph	CH=CH	470
2-(6-chloro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	471
2-(6-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	472
2-(7-chloro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	473
2-(7-chloro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	474
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	475
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	476
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	477
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	478
2-(6,7-difluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	479
2-(6,7-difluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	480
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	481
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	482
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	483
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	484
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	485
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	486
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	487
2-(6,7-difluoro)naphthyl	CH_2	1,2-Ph	CH=CH	488
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	489
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	490
3-methyl-5-fluoro indol-1-yl	SO_2	4-Cl-1,2-Ph	CH=CH	491

$R^1R^2R^3$-Het	A	X	B	Cpd
3-methyl-5-fluoro indol-1-yl	S	4-Cl-1,2-Ph	CH=CH	492
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	493
3-methyl-5-fluoro indol-1-yl	CH_2	1,2-Ph	CH=CH	494
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	495
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	496
2-(6-fluoro)quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	497
2-(6-fluoro)quinolinyl	S	4-Cl-1,2-Ph	CH=CH	498
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	499
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	500
2-(6-fluoro)quinolinyl	O	4-Cl-1,2-Ph	CH=CH	501
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	502
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	503
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	504
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	505
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	506
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	507
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	508
2-(7-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	509
2-(7-difluoromethoxy)-naphthyl	S	4-Cl-1,2-Ph	CH=CH	510
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	511
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	512
2-(7-difluoromethoxy)-aphthyl	O	4-Cl-1,2-Ph	CH=CH	513
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	514
2-(6-methoxy)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	515
2-(6-methoxy)naphthyl	S	4-Cl-1,2-Ph	CH=CH	516
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	517
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	518

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(6-methoxy)naphthyl	O	4-Cl-1,2-Ph	CH=CH	519
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	520
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	521
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	522
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	523
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	524
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	525
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	526
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	527
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	528
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	529
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	530
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	531
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	532
2-naphthyl	CH_2	4,5-Cl_2-1,2-Ph	CH=CH	533
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	534
3,4-dichlorophenyl	CH_2	4-Cl-1,2-Ph	CH=CH	535
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	536
4-chlorophenyl	CH_2	4-Cl-1,2-Ph	CH=CH	537
1-(5-phenylmethoxy) indolyl	CH_2	4-F-1,2-Ph	CH=CH	538
2-(benzo[b]thiophenyl)	CH_2	4-F-1,2-Ph	CH=CH	539
5-(1-benzyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	540
1-(6-(4-chloro)phenyl) indolyl	CH_2	4-F-1,2-Ph	CH=CH	541
1-(5-chloro)indolyl	CH_2	3,2-Pyr	CH=CH	542

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a

pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature and the

severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from about 0.5 mg to about 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 1 mg to about 2 g of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

For the treatment of any of the prostanoid mediated diseases compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, solutions, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents

selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or

condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The ability of the compounds of Formula I to interact with prostaglandin receptors makes them useful for treating, preventing or reversing undesirable symptoms caused by prostaglandins in a mammalian, especially human subject. This mimicking or antagonism

of the actions of prostaglandins indicates that the compounds and pharmaceutical compositions thereof are useful to treat, prevent or ameliorate prostaglandin mediated diseases and conditions in mammals and especially in humans: Pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures as well as immune and autoimmune diseases. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention prostaglandin-mediated proliferation disorders such as may occur in diabetic retinopathy and tumor angiogenesis. Compound I will also inhibit prostanoid-induced smooth muscle contraction by antagonizing contractile prostanoids or mimicking relaxing prostanoids and hence may be use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, the treatment of glaucoma, for the prevention of bone loss (treatment of osteoporosis) and for the promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

By virtue of its prostanoid or prostanoid antagonist activity, compound I will prove useful as an alternative to NSAID'S particularly where such non-steroidal anti-inflammatory drugs may be contraindicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; thrombosis, occlusive vascular diseases; those prior to surgery or taking anti-coagulants. Compound I

will also be useful as a cytoprotective agent for patients under chemotherapy.

Compound of Formula I, will be useful as a partial or complete substitute for conventional antiinflammatory or analgesic compounds in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating prostaglandin E_2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a COX-2 selective NSAID; a conventional NSAID; a potentiator including caffeine; an H_2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; another prostaglandin ligand including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol; a diuretic; a sedating or non-sedating antihistamine. In addition, the invention encompasses a method of treating prostaglandin E_2 mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Compounds of the present invention can be prepared according to the following methods. Temperatures are in degrees Celsius.

Boronic acids and esters can be prepared from the corresponding halide according to literature procedure and reference cited therein (Charette, A.B.; Giroux, A. J. Org. Chem. 1996, 61, 8718; Ishiyama, T.; Murata, M.; Miyaura, N. J. Org. Chem. 1995, 60, 7508; Miyaura, N.; Suzuki, A. Chem. Rev, 1995, 95, 2457; Murata, M.; Watanabe, S.; Masuda, Y. J. Org. Chem. 1997, 62, 6458; Watanabe, T.

Miyaura, N.; Suzuki, A. Synlett, 1992, 207; Maddaford, S.; Keay, B.A. J. Org. Chem. 1994, 59, 6501; Cristofoli, W.A.; Keay, B.A. Tetrahedron Lett. 1991, 32, 5881; Passafaro, M.S.; Keay, B.A. . Tetrahedron Lett. 1996, 37, 429; Serafin, B.; Makosza, M. Tetrahedron, 1963, 19, 821). In some cases, the triflate, the tin or the zinc derivatives may be used instead of the boronic acid.

Method A

Cinnamic ester **1** is treated with a brominating agent such as NBS in a refluxing inert solvent such as CCl_4, with the use of an initiator like benzoyl peroxide or light. The resulting benzylic bromide is reacted in a Suzuki coupling reaction with the appropriate boronic acid or ester, a catalyst such as tetrakis(triphenylphosphine) palladium and cesium fluoride or Na_2CO_3 or a base in an inert refluxing solvent such as DME at 80-90^0 C. The new cinnamic ester **3** is hydrolyzed with aqueous sodium hydroxide to afford the acid **4** that is converted to the cinnamic sulfonamide **5** with a coupling reagent such as DCC or DCI in CH_2Cl_2 at r.t.

Method B

Cinnamic ester **2** is treated with an aryl or heteroaryl mercaptan, alcohol or amine, and with a base such as a hydride or an amine in benzene or THF at 0-23° C. The resulting cinnamic ester **6** is converted to **7** according to Method A.

If W= sulfur, it is oxidized to the sulfoxide or sulfone **8** with hydrogen peroxide, m-CPBA or other peracetic acid. The cinnamic ester **8** is converted to **9** according to Method A.

Method C

The aldehyde **11** is prepared by an addition-elimination of a mercapto, hydroxy or amino aryl or heteroaryl with a base such as K_2CO_3 in refluxing $CHCl_3$. If needed a higher boiling point solvent can be used. This type of rection can also be performed with CuO in DMF. An Emmons-Horner type reaction (or Wittig) in toluene at r.t. followed by Method A (or oxidation as described in Method B) results in the cinnamic sulfonamide **13**.

Method D

Acetal **14** that came from an acetalization from a suitably substituted bromo benzaldehyde is converted to the Grignard reagent with magnesium in an etheral solvent at reflux and quenched with an aryl or heteroaryl ketone. The alcohol **16** is reacted with an halide and a base (or protected as the *o*-nitrobenzyl, and removed at the end of the sequence) to furnish the compound **17**. Deprotection of the acetal under standard conditions followed by Method C gives **18**.

Method E

Alcohol **16** is converted to an acetate with acetyl chloride (or acetic anhydride and an amine base) and coupled with a Grignard reagent and a copper salt at low temperature. The alcohol **16** could also be converted to the bromide and treated in a similar way to yield **20**. Alternatively the tetrametyl acetal (R= methyl) version of alcohol **16** can be treated with $TiCl_4/Me_2Zn$ (or $R^7{}_2Zn$) at -30 °C. Compound **20** is then

converted to the cinnamic sulfonamide **21** according to Method D. Also, **22** can be treated with $Al(R^7)_3$ in toluene at 80 °C for 24h and **23** converted to the aldehyde with n-BuLi/DMF followed by an Emmons-Horner reaction and Method A to yield compound **21**.

Method F

A suitably substituted bromo toluene **24** is treated with n-Buli at low temperature and quenched with an aryl or heteroaryl aldehyde. The resulting alcohol is oxidized to the ketone with PDC, PCC, MnO_2 or other typical oxidizing agent. The carbonyl is treated with SF_4, MoF_6-BF_3 (or converted to a thioacetal and treated with nitrosonium BF_4-pyridinium•HF) to yield the difluoride. Benzylic bromination with NBS followed by oxidation with N-methylmorpholine N-oxide at 100 °C in dioxane for 4 h, yielded compound **25** that is converted to cinnamic sulfonamide **26** with Method C.

Method G

The appropriately substituted methyl bromo(or triflate) benzoate **27** is converted to compound **28** by a Suzuki coupling reaction followed by hydrogenation. A Stille coupling reaction could also be used. Benzylic bromination or benzylic oxidation followed by treatment with a brominating agent such as CBr_4/triphenylphosphine gives compound **29** which can be treated with a boronic acid, or a tin compound (Stille) to furnish compound **30**. Reduction of the ester with DIBAL, oxidation with MnO_2 and Method C gives compound **31**.

Method H

Compound **29** (one R^7 = H) is treated with triphenyl phosphine to give the salt and, with a base such as LDA, is converted to compound **32** with the aryl or heteroaryl ketone. The halide **29** can also be converted the Grignard reagent and added to the ketone. Dehydration under acidic conditions results in compound **32**. Reduction of the double bond under standard conditions, followed by Methods G and C gives compound **33**. From compound **32**, cyclopropanation with

diazomethane and palladium (0) followed by Methods G, C and A gives compound **34**.

Method I

The (heterocyclic) vinylic bromide **35** is reacted in a Suzuki coupling reaction with an aryl or hetero aryl boronic acid and converted to a new borane by 9-BBN addition followed by a second Suzuki reaction with compound **14**. Compound **37** thus formed is reduced by hydrogenolysis (H_2/metal or diimide) and deprotection followed by Method C gives cinnamic sulfonamide **39**.

Method J

Ketone **40** which comes from oxidation of the corresponding alcohol is reacted with a phosphonium salt or phosphono ester with a base such as LDA to give the cinnamic ester **41**. Method A yields **42** and reduction of the double bond by the previously mentioned method gives the acyl sulfonamide **43**.

Method K

Cinnamic ester **3** is reduced to **44** by the previously mentioned method. α Alkylation with a base such as LDA followed by an alkylating agent results in **45** after conversion to the acyl sulfonamide.

Method L

Cinnamic ester **3** is reduced to **46** with DIBAL and the double bond converted to a cyclopropane by a Simmons-Smith reaction, or similar reactions recently described in the literature. Compound **47** is then oxidized and the cinnamic sulfonamide **48** is prepared according to Method A.

Method M

Ester **49** which can come from the homologation of the appropriately substituted methyl ortho-toluate, is treated with a base and with an alkylating agent to furnish compound **50**. Benzylic bromination and Suzuki coupling gives an intermediate ester. Homologation according to *J. Amer. Chem. Soc.*; **1985**, 1429; J. Org. Chem. **1992**, 7194,

followed by alkylation with a base such as LDA and an alkylating agent furnishes acylsulfonamide **51** by Method A.

Compound **50** can also be converted to the benzylic bromide and to compound **52** by Method A.

Method N

Suitably substituted compound **53** is treated with a boronic acid to give compound **54** which is reduced with LDA to the alcohol **55**. Treatment with phosgene followed with the appropriate sulfonamide gives compound **56**. This can also be prepared by mixing phosgene and the sulfonamide at 140°C to generate the isocyanate.

Compound **54** is treated with a Grignard reagent to give the corresponding alcohol and as previously described, converted to compound **57**.

Method O

Ester **58** is treated with Lawesson's reagent, DAST and light to give the benzylic alcohol **59**. The procedure according to Method N yields compound **60**.

Method P

Compound **59** is brominated as described earlier (or iodinated) and reacted in a S_N2 type reaction with an ester and a base such as LDA to furnish ester **61**. Method A gives the acylsulfonamide **62**.

Method Q

Compound **55** is treated with NH_3/Ph_3P/DEAD (or treated with CBr_4/Ph_3P and the bromide converted to the amine **63** with ammonia). Treatment with phosgene followed by sulfonamide yields **64**, treatment of which with a base and an alkyl or benzylic halide gives compounds **65**.

Method R

Aldehyde **10** is treated with a silylated source of hydroxyl or thiol at 80-130 °C, and the silyl group removed by fluoride treatment. Compound **66** is then treated with an aryl or heteroaryl methylene bromide with a base such as a tertiary amine in $CHCl_3$ or benzene to yield aldehyde **67**. Emmons-Horner (or Wittig reaction) with LDA results in compound **68** via Method A.

Method S

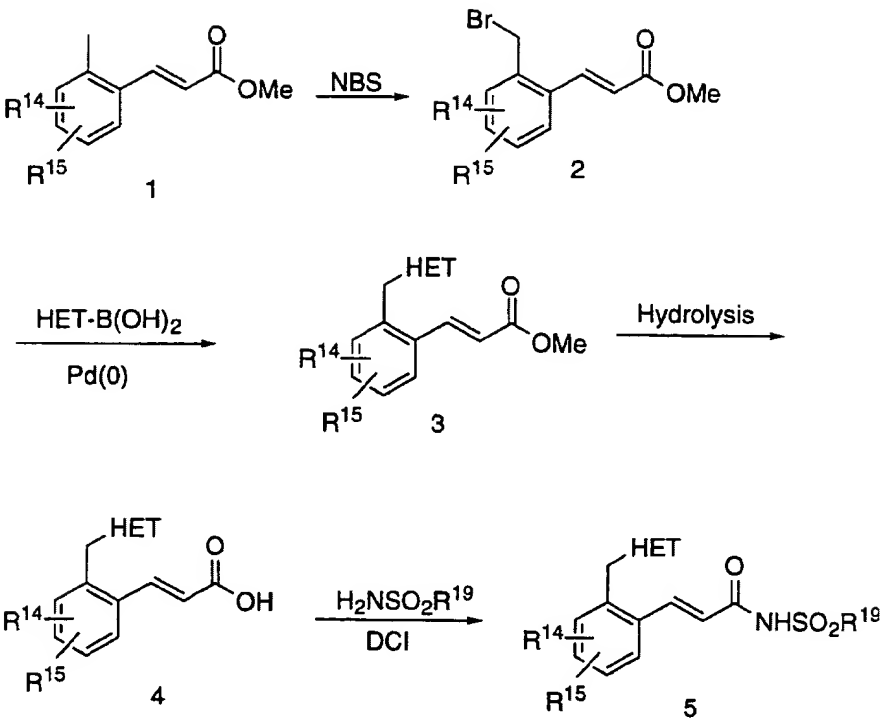
In the case of an amine an alternative to method R can be used. A suitably substituted nitro aldehyde **69** is converted to compound **70** as described earlier and the nitro group reduced with standard methods. Mono-alkylation followed by displacement with an aryl or heteroaryl methylene bromide and processing by Method A yields cinnamic sulfonamide **71**.

Method T

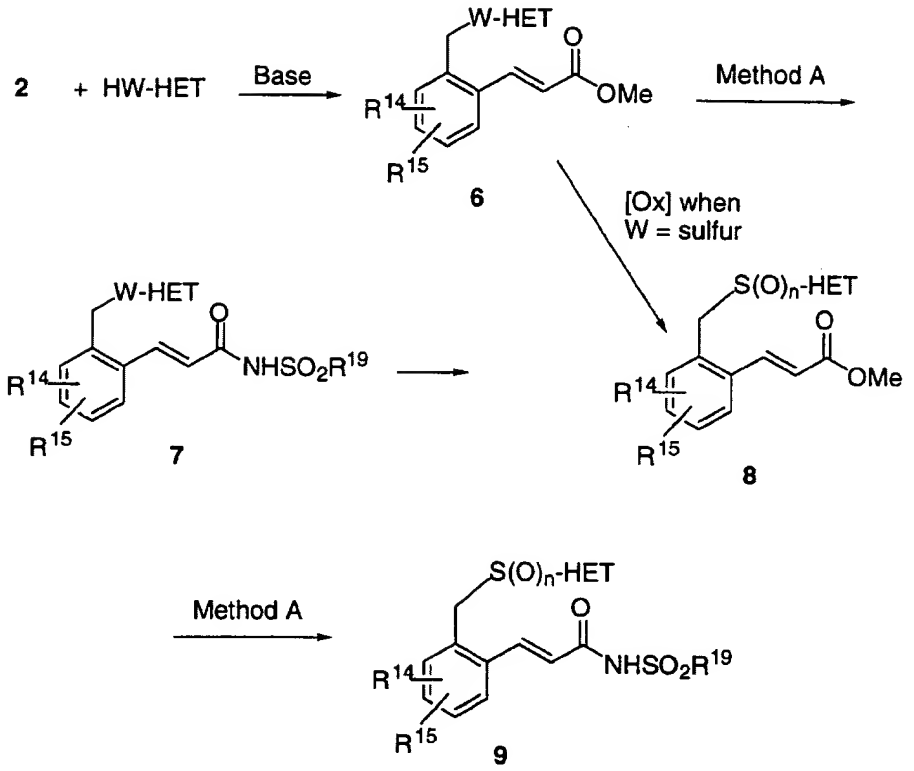
A suitably substituted bromo toluene **24** is converted to the anion in an etheral solvent at low temperature and trapped with an aldehyde of an aryl or heteroaryl. The resulting alcohol is oxidized with MnO_2, Jones' reagent, PDC, PCC or any other oxidant. Benzylic bromination followed by oxidation with N-methyl morpholine N-oxide, yields a ketoaldehyde. Emmons-Horner and Method A gives the cinnamic sulfonamides **72**.

Generic structures 4, 5, 7, 9, 13, 18, 21, 26, 31, 33, 34, 39, 42, 43, 45, 48, 51, 52, 56, 57, 60, 62, 64, 65, 68, 71 and 72 are representative of the compounds of the present invention. It is also noted that where the chemistry allows in the generic schemes, alternate embodiments of -A-, such as heteroaryl groups, can be substituted for phenyl in the schemes.

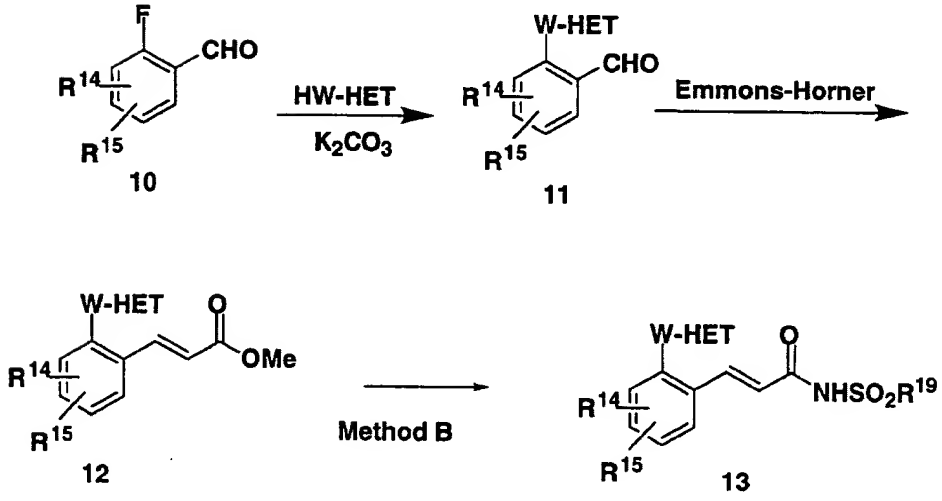
Method A


Br
O
OMe
NBS
R^{14}
R^{15}
1
2
HET
HET-B(OH)$_2$
Pd(0)
Hydrolysis
3
OH
$H_2NSO_2R^{19}$
DCI
$NHSO_2R^{19}$
4
5

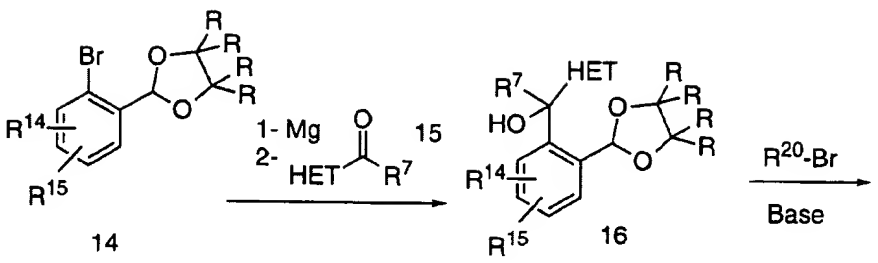
Method B



Method C

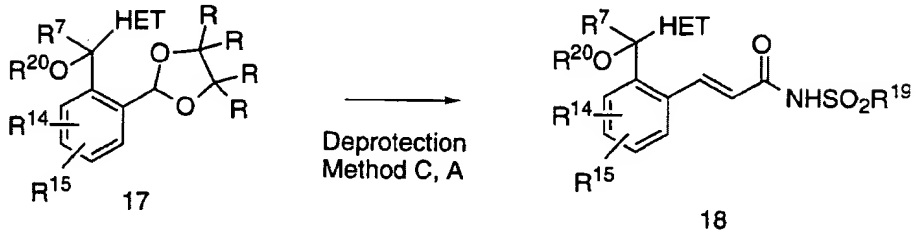


Method D

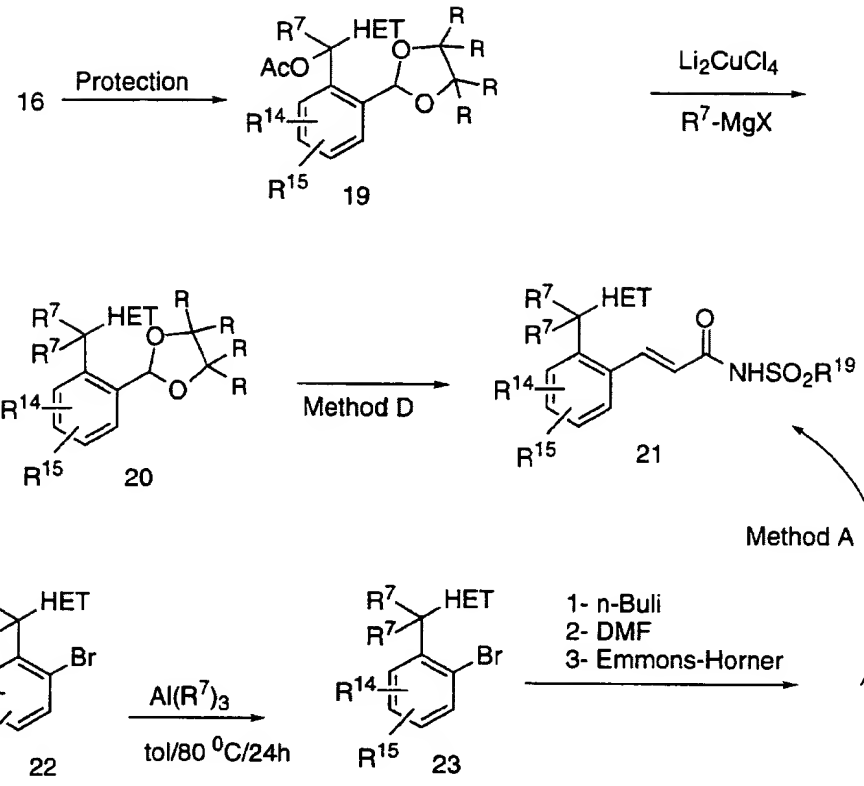


14

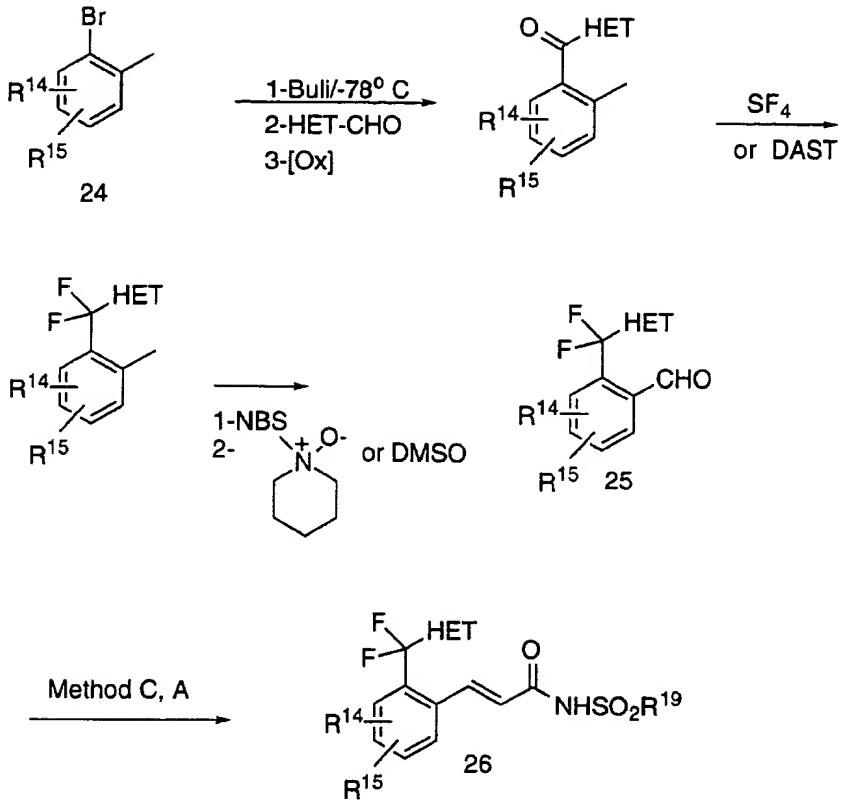
R= H, Methyl



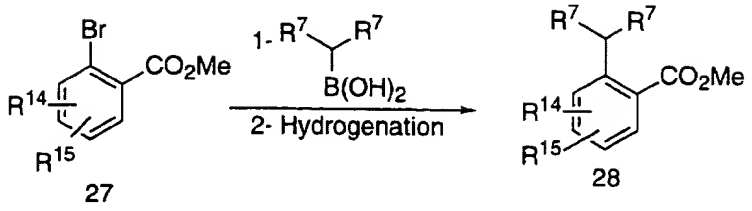
Method E


16
Protection
R7
HET
AcO
R14
R15
19
R
Li2CuCl4
R7-MgX
20
Method D
NHSO2R19
21
Method A
22
Al(R7)3
tol/80 0C/24h
23
1- n-Buli
2- DMF
3- Emmons-Horner

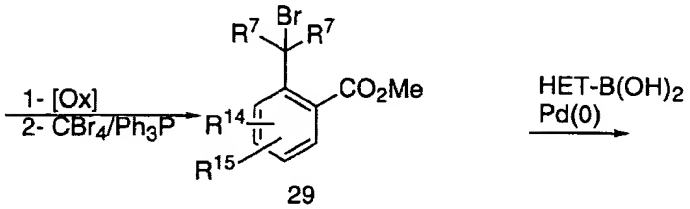
Method F


Br
R14
R15
24
1-BuLi/-78° C
2-HET-CHO
3-[Ox]
O
HET
R14
R15
SF4
or DAST
F
F
HET
R14
R15
1-NBS
2-
or DMSO
F
F
HET
CHO
R14
R15
25
Method C, A
F
F
HET
O
NHSO2R19
R14
R15
26

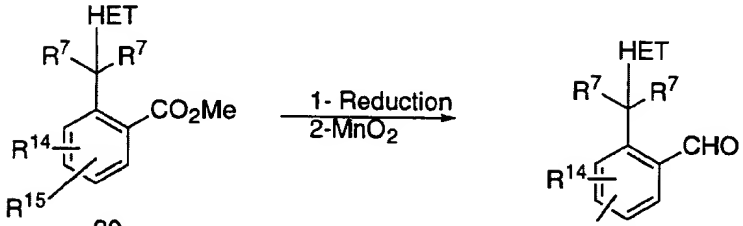
Method G



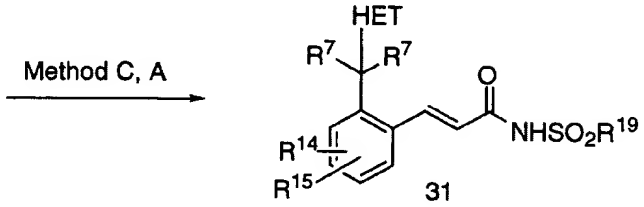
27 28



29

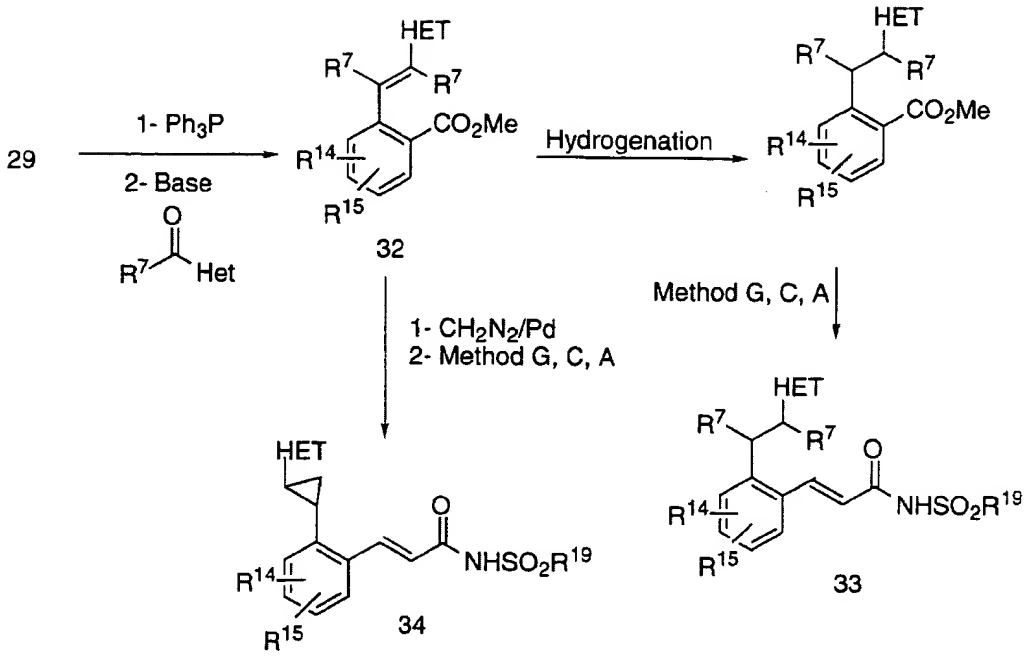


30 30a

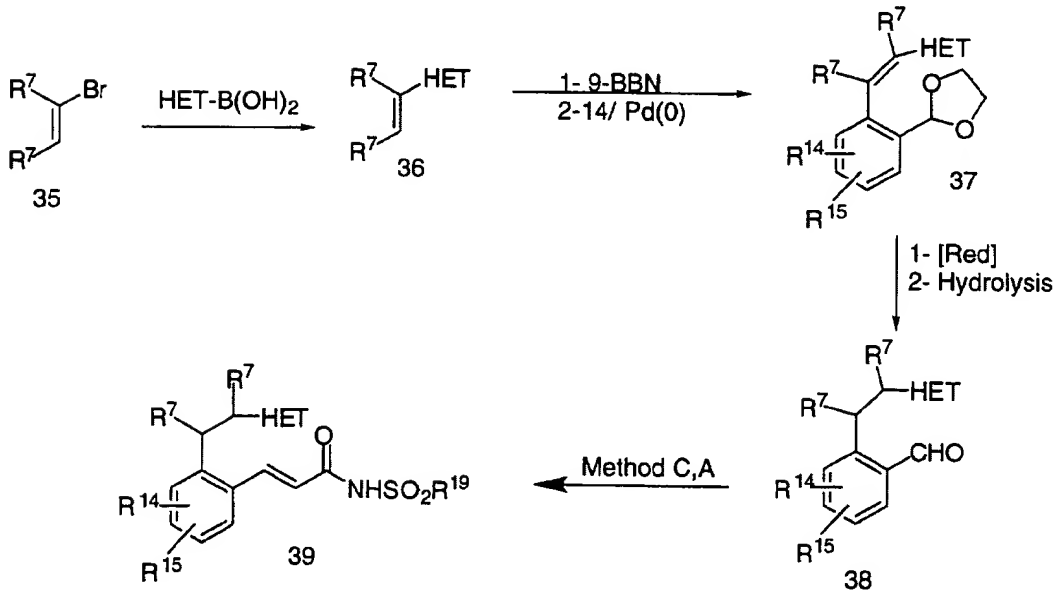


31

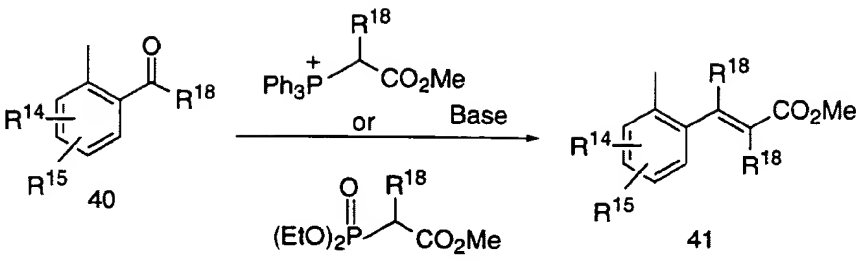
Method H

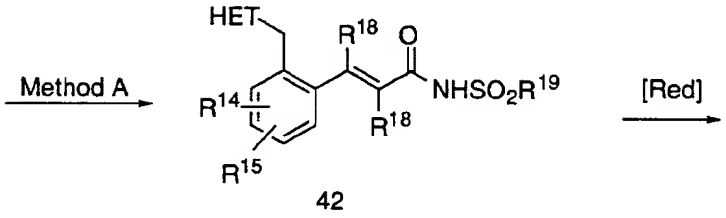


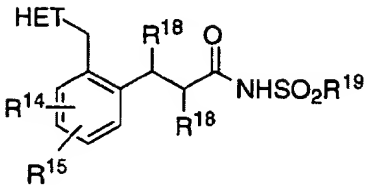
Method I



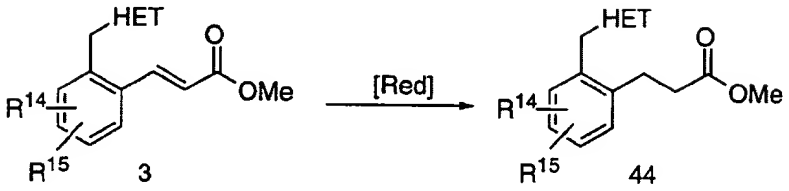
Method J

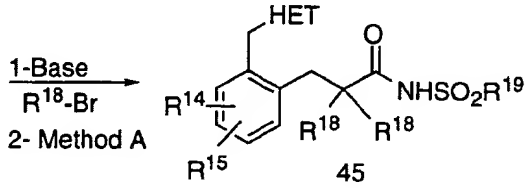




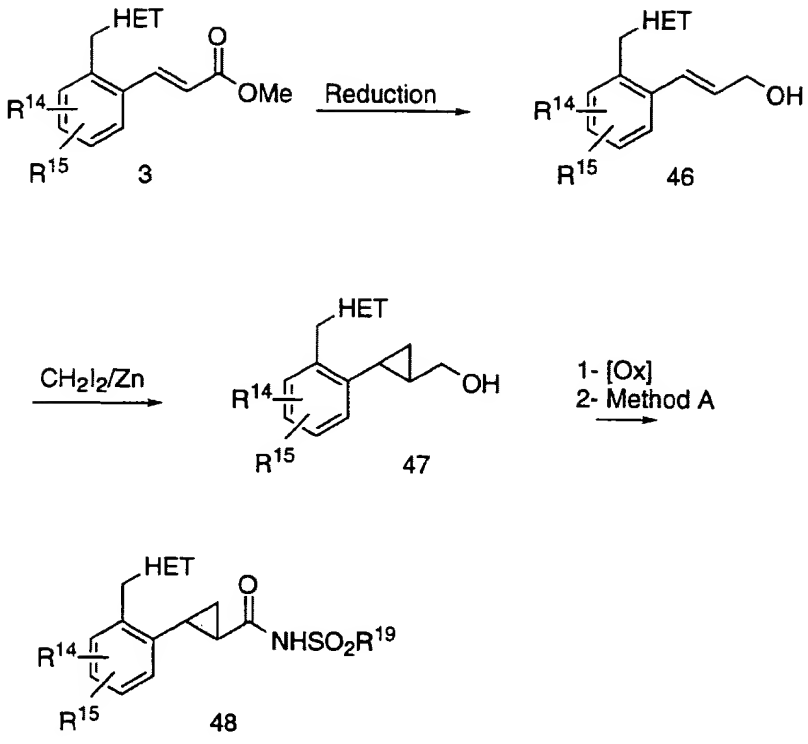


Method K

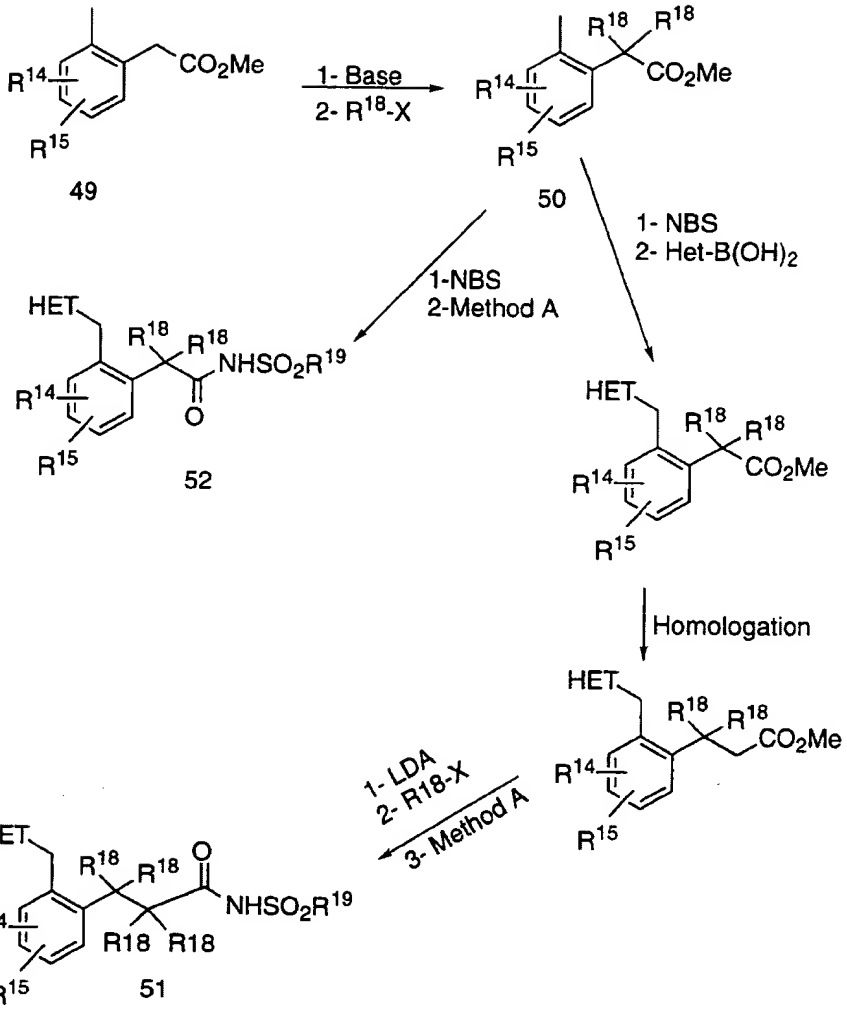




Method L

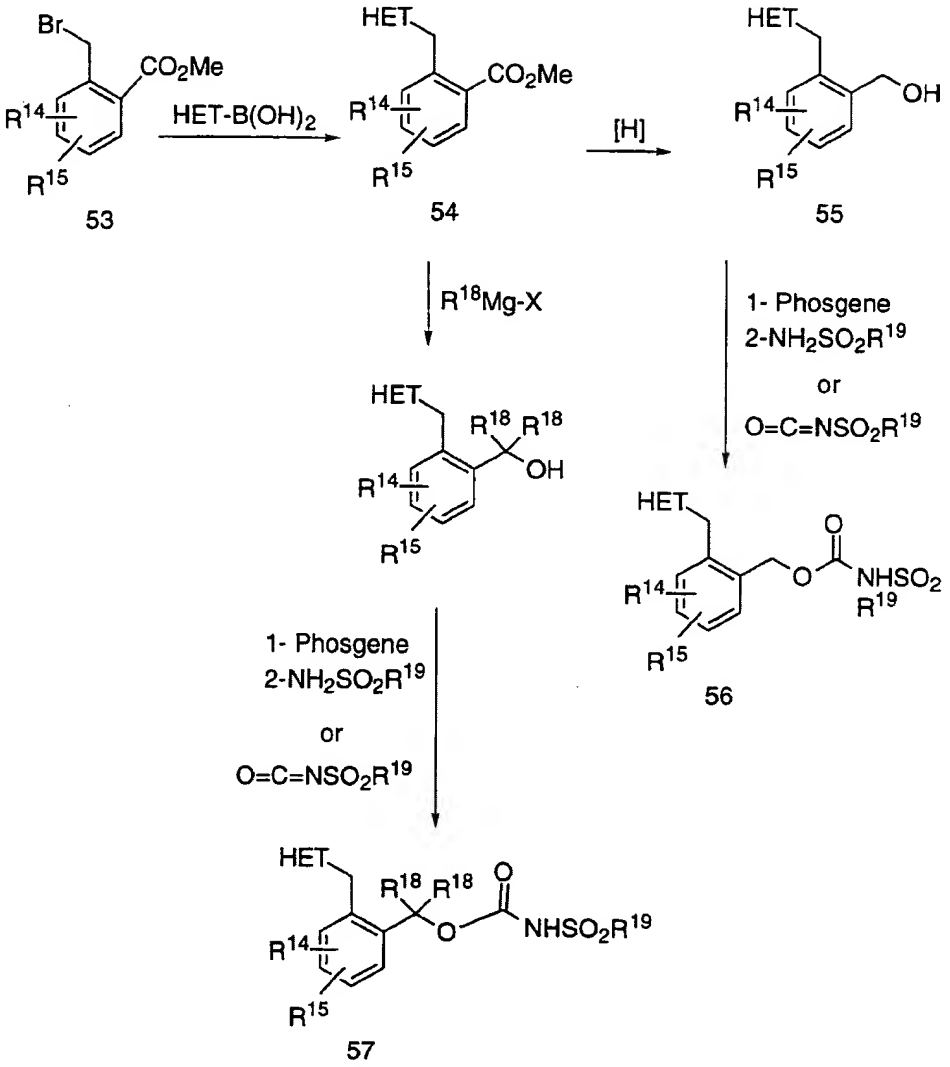

HET
O
OMe
Reduction
R^{14}
R^{15}
3
HET
OH
R^{14}
R^{15}
46
CH_2I_2/Zn
HET
OH
R^{14}
R^{15}
47
1- [Ox]
2- Method A
HET
O
$NHSO_2R^{19}$
R^{14}
R^{15}
48

Method M

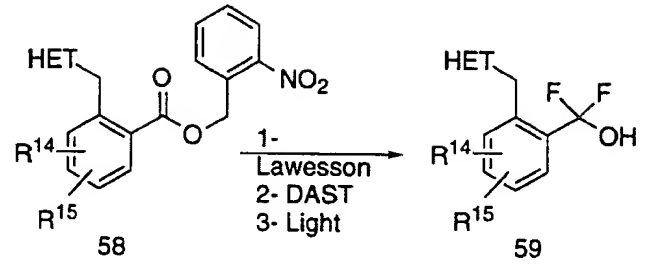

R14
R15
CO2Me
1- Base
2- R18-X
R18
R18
CO2Me
49
50
1- NBS
2- Het-B(OH)2
1-NBS
2-Method A
HET
R18
R18
NHSO2R19
O
52
HET
R18
R18
CO2Me
Homologation
HET
R18
R18
CO2Me
1- LDA
2- R18-X
3- Method A
HET
R18
R18
O
NHSO2R19
R18
R18
51

5

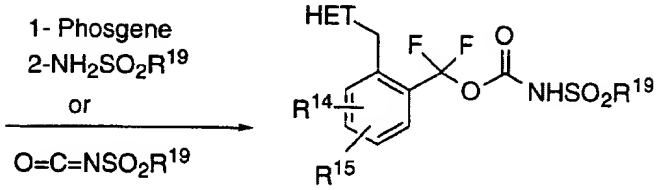
Method N


Br
CO2Me
R14
R15
HET-B(OH)2
HET
CO2Me
[H]
OH
53
54
55
R18Mg-X
1- Phosgene
2-NH2SO2R19
or
O=C=NSO2R19
R18 R18
NHSO2
R19
56
57

Method O

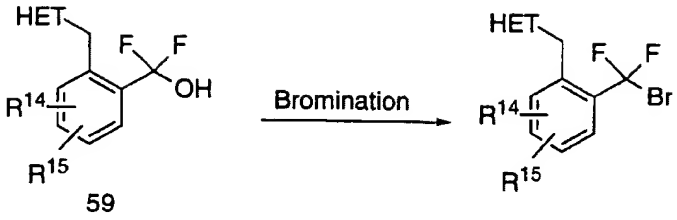


58 59



60

Method P



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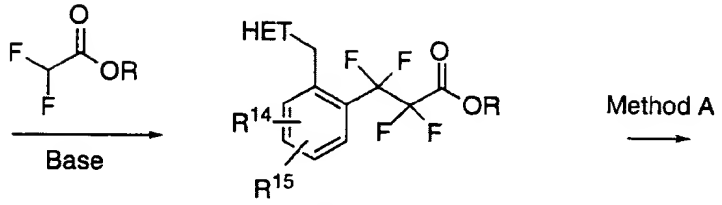

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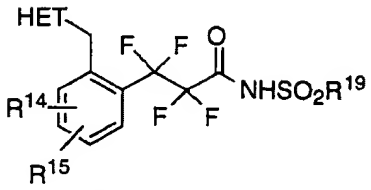

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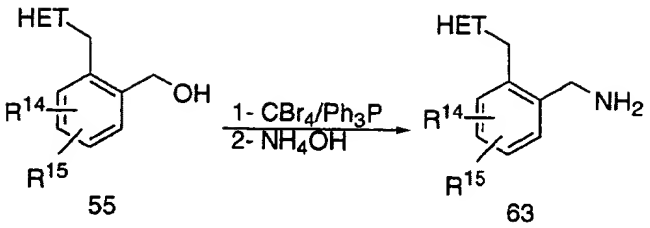
Method Q



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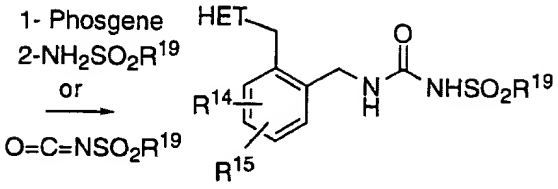

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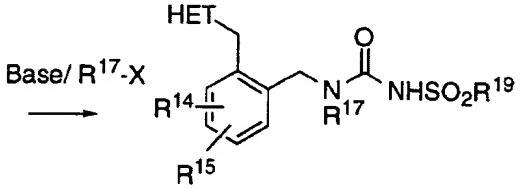
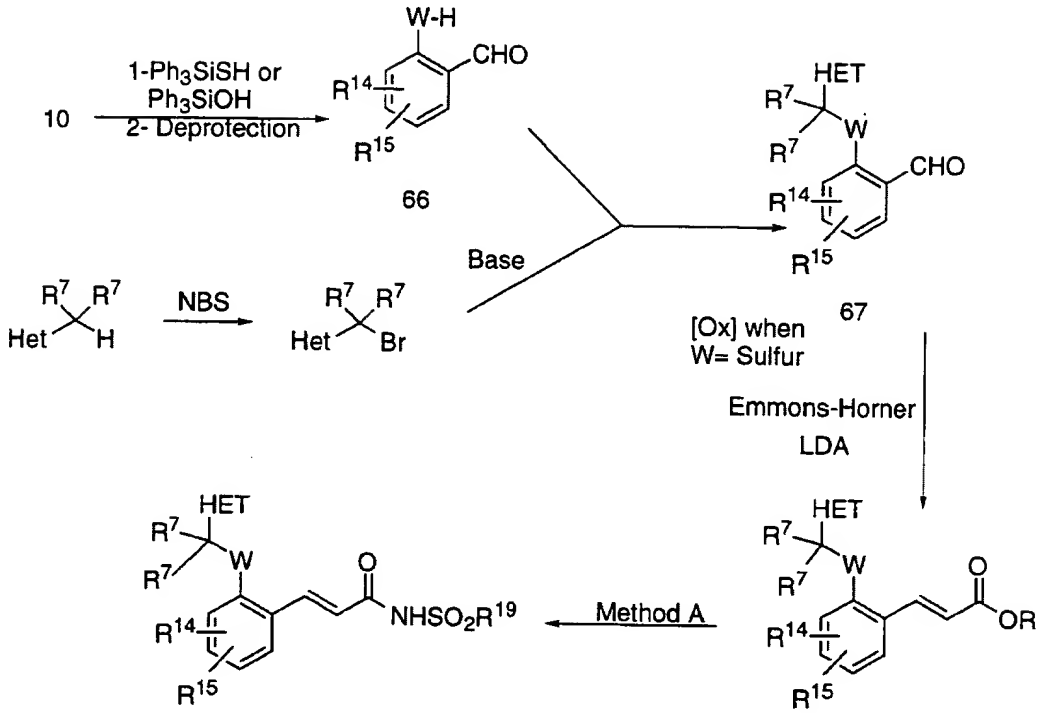
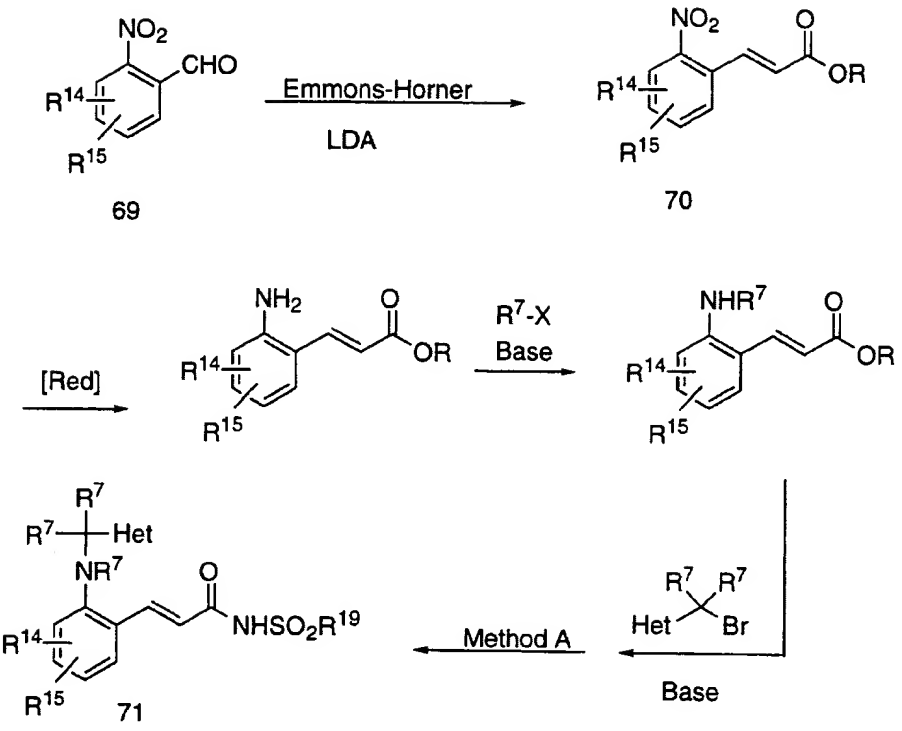


65

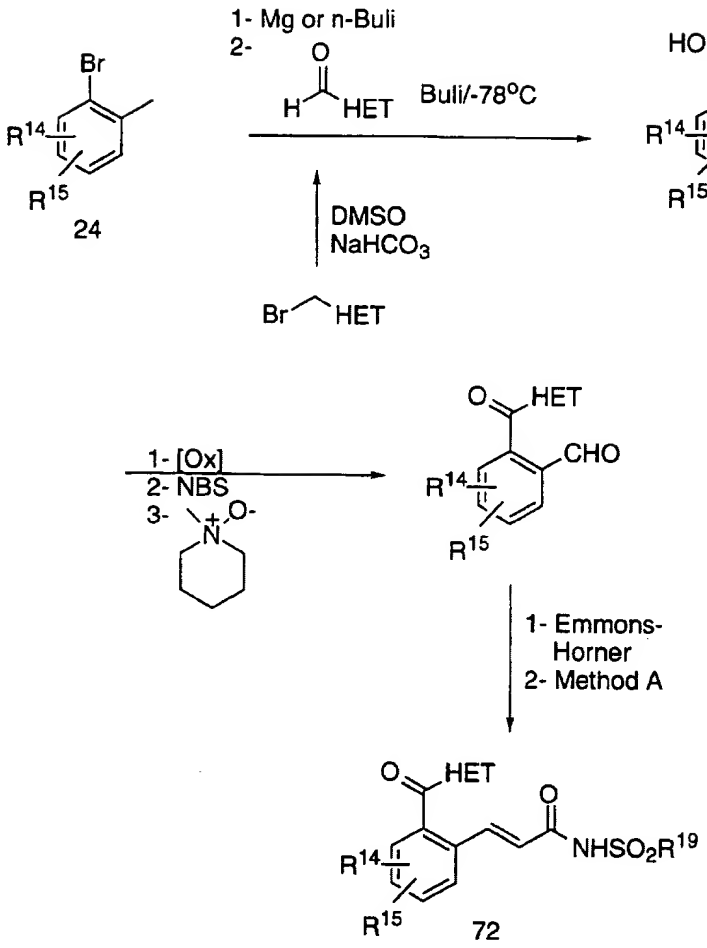
Method R


W-H
CHO
1-Ph3SiSH or
Ph3SiOH
2- Deprotection
10
R14
R15
66
HET
R7
R7
W
CHO
R14
R15
67
Base
NBS
Het
H
Br
[Ox] when
W= Sulfur
Emmons-Horner
LDA
O
OR
Method A
NHSO2R19
68

Method S


NO2
CHO
R14
R15
69
Emmons-Horner
LDA
NO2
O
OR
R14
R15
70
[Red]
NH2
O
OR
R14
R15
R7-X
Base
NHR7
O
OR
R14
R15
R7
R7
Het
NR7
O
NHSO2R19
R14
R15
71
Method A
R7
R7
Het
Br
Base

Method T



ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

Biological activity and thus utility for the compounds of formula I as modulators of prostaglandin mediated diseases can be demonstrated in accordance with the following assayswhich demonstrate prostanoid antagonist or agonist activity *in vitro* and *in vivo* and their selectivity. The prostaglandin receptors investigated were DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

Stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293(ebna) cell line

Prostanoid receptor cDNAs corresponding to full length coding sequences were subcloned into the appropriate sites of mammalian expression vectors and transfected into HEK 293(ebna) cells. HEK 293(ebna) cells expressing the individual cDNAs were grown under selection and individual colonies were isolated after 2-3 weeks of growth using the cloning ring method and subsequently expanded into clonal cell lines.

Prostanoid receptor binding assays

HEK 293(ebna) cells are maintained in culture, harvested and membranes are prepared by differential centrifugation, following lysis of the cells in the presence of protease inhibitors, for use in receptor binding assays. Prostanoid receptor binding assays are performed in 10 mM MES/KOH (pH 6.0) (EPs, FP and TP) or 10 mM HEPES/KOH (pH 7.4) (DP and IP), containing 1 mM EDTA, 10 mM divalent cation and the appropriate radioligand. The reaction is initiated by addition of membrane protein. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. Non-specific binding is determined in the presence of 1 μM of the corresponding non-radioactive prostanoid. Incubations are conducted for 60 min at room temperature or 30 °C and terminated by rapid filtration. Specific binding is calculated by subtracting non specific binding from total binding. The residual specific binding at each ligand concentration is calculated and expressed as a function of ligand concentration in order to construct sigmoidal concentration-response curves for determination of ligand affinity.

Prostanoid receptor agonist and antagonist assays

Whole cell second messenger assays measuring stimulation (EP_2, EP_4, DP and IP in HEK 293(ebna) cells) or inhibition (EP_3 in human erythroleukemia (HEL) cells) of intracellular cAMP accumulation or mobilization of intracellular calcium (EP_1, FP and TP in HEK 293(ebna) cells stably transfected with apo-aequorin) are performed to determine whether receptor ligands are agonists or

antagonists. For cAMP assays, cells are harvested and resuspended in HBSS containing 25 mM HEPES, pH 7.4. Incubations contain 100 μM RO-20174 (phosphodiesterase type IV inhibitor, available from Biomol) and, in the case of the EP_3 inhibition assay only, 15 μM forskolin to stimulate cAMP production. Samples are incubated at 37°C for 10 min, the reaction is terminated and cAMP levels are then measured. For calcium mobilization assays, cells are charged with the co-factors reduced glutathione and coelenterazine, harvested and resuspended in Ham's F12 medium. Calcium mobilization is measured by monitoring luminescence provoked by calcium binding to the intracellular photoprotein aequorin. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. For agonists, second messenger responses are expressed as a function of ligand concentration and both EC_{50} values and the maximum response as compared to a prostanoid standard are calculated. For antagonists, the ability of a ligand to inhibit an agonist response is determined by Schild analysis and both K_B and slope values are calculated.

Rat Paw Edema Assay

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, 1995).

LPS-Induced Pyrexia in Conscious Rats

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, 1995).

LPS-Induced Pyrexia in Conscious Squirrel Monkeys

The method is the same as described in Chan *et al* (Eur. J. Pharmacol. 327: 221- 225, 1997).

Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

The method is the same as described in Boyce *et al* (Neuropharmacology 33: 1609-1611, 1994).

Adjuvant-Induced Arthritis in Rats

Female Lewis rats (body weight ~146-170 g) were weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.10-3.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 mL of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were determined before (day -1) and 21 days following adjuvant injection, and primary paw volumes were determined before (day -1) and on days 4 and 21 following adjuvant injection. The rats were anesthetized with an intramuscular injection of 0.03 - 0.1 mL of a combination of Ketamine (87 mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs were made of both hind paws on day 0 and day 21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were developed in an automatic processor. Radiographs were evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes were graded numerically according to severity: increased soft issue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria were used to establish the numerical grade of severity for each radiographic change. The maximum possible score per foot was 26. A test compound at total daily doses of 0.1, 0.3, 1, and 3 mg/kg/day, indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were

prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

The invention is illustrated in connection with the following non-limiting Examples. All the end products of the formula I were analyzed by NMR, TLC and mass spectrometry.

Intermediates were analyzed by NMR and TLC.

Most compounds were purified by flash chromatography on silica gel. Recrystallization and/or swish (suspension in a solvent followed by filtration of the solid) with a solvent such as ether:hexane 1:1.

The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only.

Temperatures are in degrees Celsius.

The compounds of the examples are numbered in accordance with the compounds that appear in Tables I and II.

EXAMPLE 1

N-((E)-3-{2-[4-(METHYLTHIO)BENZYL]PHENYL}-2-PROPENOYL)-2-THIOPHENESULFONAMIDE (17)

Step 1: Methyl (E)-3-(2-methylphenyl)-2-propenoate

To 2-methylcinnamic acid (100g; 617 mmol) in 1.2 L of DMF was added DBU (112.6 g; 740 mmol) and 15 min later methyl iodide (131.3 g; 925 mmol) and left overnight. The solution was diluted in ether and washed with HCl (10%), H_2O and brine. The solvent was removed to give 106.8 g of the title compound.

^1H NMR ($CDCl_3$) δ 2.4 (3H, s), 3.8 (3H, s), 6.35 (1H, d), 7.15 (1H, t), 7.22 (1H, t), 7.5 (1H, d) and 7.95 (1H, d).

The ethyl ester can be prepared as well in the same way or from the 2-methyl benzaldehyde (5.00 g; 41.6 mmol) and triethyl phosphonoacetate (9.9 mL; 50.0 mmol) in 150 mL ot toluene at 0 °C, to which was added portionwise NaH (63.0 mmol). After 2 h of stirring the mixture was quenched with NH_4OAc (25%) and extracted with EtOAc. The solvent was removed to give 7.1 g of the ethyl cinnamate.

Step 2: Ethyl (E)-3-[2-(bromomethyl)phenyl]-2-propenoate

To the previous ethyl cinnamate (20.0 g; 105 mmol) and NBS (19.64 g; 110.3 mmol) in refluxing CCl_4 was added benzoyl peroxide (1.27 g) and the mixture was stirred for 12 h. The solution was cooled to r.t. and filtered. The solvent was removed and the crude oil purified by silica gel chromatography (5% EtOAc in hexane) to yield 14.18 g of the title compound.

^1H NMR ($CDCl_3$) δ 1.30 (3H, t), 4.25 (2H, q), 4.60 (2H, s), 6.45 (1H, d), 7.30 (3H, m), 7.57 (1H, m) and 8.05 (1H, d).

Step 3: Ethyl (E)-3-[2-[4-(methylthio)benzyl]phenyl]-2-propenoate

A mixture of the previous benzyl bromide (0.50 g; 1.86 mmol), 4-(methylthio)benzeneboronic acid (0.63 g; 3.7 mmol) CsF (1.13 g) and ($Ph_3P)_4Pd$ (0.11 g) in 10 mL of DME was heated to reflux for 10 h. The mixture was cooled to r.t. and quenched with NH_4OAc (25%) and extracted with EtOAc. The organic phases were combined, dried and the solvent removed. Purification by silica gel chromatography (10% EtOAc in hexane) yielded 0.35 g of the title compound.

^1H NMR ($CDCl_3$) δ 1.27 (3H, t), 2.41 (3H, s), 4.08 (2H, s), 4.21 (2H, q), 6.30 (1H, d), 7.00 (1H, d), 7.1-7.4 (6H, m), 7.55 (1H, d) and 7.97 (1H, d).

Step 4: (E)-3-[2-[4-Methylthio)benzyl]phenyl]-2-propenoic acid

Hydrolysis of the previous ester (0.34 g; 1.1 mmol) was run in THF/MeOH (6 mL/3 mL) with 2 equivalent of a 2N NaOH solution for 4 h. The solution was diluted with EtOAc and quenched with HCl (10%). The organic phase was dried over Na_2SO_4 and the solvent removed. Purification was done by a swish in hexane to yield 0.21 g of the title compound.

^1H NMR ($CDCl_3$) δ 2.42 (3H, s), 4.09 (2H, s), 6.31 (1H, d), 7.00-7.35 (7H, m), 7.50 (1H, d) and 8.07 (1H, d).

Step 5: N-((E)-3-[2-[4-(methylthio)benzyl]phenyl]-2-propenoyl)-2-thiophenesulfonamide (17)

2-Thiophenesulfonamide was prepared from the corresponding sulfonyl chloride with 2.2 equivalent of NH_4OH in THF at 0 °C. The solution was brought to r.t. and left 2 h. It was then quenched with $NaHCO_3$ and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent removed. The crude product was crystallized in toluene/EtOAc.

To the previous acid (100 mg; 0.35 mmol), 2-thiophenesulfonamide (60 mg; 0.37 mmol), DMAP (86 mg; 0.7 mmol) in 2 mL of CH_2Cl_2 was added DCI (134 mg; 0.7 mmol) and the mixture was stirred overnight. The solution was diluted with EtOAc and quenched

with HCl (10%). The organic phase was dried over Na_2SO_4 and the solvent removed. Purification by silica gel chromatography (5% MeOH in CH_2Cl_2) yielded 87 mg of the title compound.

^1H NMR ($CDCl_3$) δ 2.40 (3H, s), 4.01 (2H, s), 6.33 (1H, d), 6.9-7.3 (8H, m), 7.49 (1H, d), 7.61 (1H, s), 7.89 (1H, s) and 8.03 (1H, d). The product was converted to the sodium salt with 1 equivalent of NaOH and freeze dried.

Elemental analysis calcd. for $C_{21}H_{18}NNaO_3S_3.1/2H_2O$: C, 54.77; H, 4.13; N, 3.04; S, 20.88; Found: C, 54.55; H, 4.01; N, 3.06; S, 20.58.

EXAMPLE 2

N-((E)-3-{2-[(3-METHYL-1H-1-INDOLYL)METHYL]PHENYL}-2-PROPENOYL)-2-THIOPHENESULFONAMIDE (3)

Step 1: Ethyl (E)-3-{2-[(3-methyl-1H-1-indolyl)methyl]phenyl}-2-propenoate

To benzylic bromide (400 mg, 1.49 mmol) of step 2 in example 1 and skatole (200mg, 1.51 mmol) in 6 mL of DMF was added portionwise 1.6 equivalent of NaH. The reaction mixture was left for 6 h and quenched with NH_4OAc (25%) and diluted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and the solvent removed. Purification by silica gel chromatography (10% EtOAc inhexane) yielded 260mg of the title compound.

^1H NMR ($CDCl_3$) δ 1.2 (3H, t), 2.3 (3H, s), 4.25 (2H, q), 5.4 (2H, s), 6.35 (1H, d), 6.65 (1H, d), 6.8 (1H, s), 7.1-7.3 (5H, m), 7.56 (2H, d) and 7.97 (1H, d).

Step 2: (E)-3-{2-[(3-methyl-1H-1-indolyl)methyl]phenyl}-2-propenoic acid

The hydrolysis of the previous ester (260 mg) was done according to Step 4 of example 1 to yield 212 mg of the title compound.

HRMS calcd. for $C_{19}H_{17}NO_3 + H^+ = 292.1337$; Found: 292.1337.

Step 3: N2-((E)-3-{2-[(3-methyl-1H-1-indolyl)methyl]phenyl}-2-propenoyl)-2-thiophenesulfonamide (3)

The coupling reaction of the previous acid (196 mg; 0.67 mmol) was done according to step 5 of example 1 to yield 134 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 2.39 (3H, s), 5.57 (2H, s), 6.65 (2H, m), 7.03 (3H, m), 7.27 (4H, m), 7.5 (1H, d), 7.63 (1H, d), 7.87 (1H, d), 7.95 (1H, s) and 8.14 (1H, d).

HRMS calcd. for $C_{23}H_{20}N_2O_3S_2 + H^+ = 437.0994$; Found: 437.0992.

EXAMPLE 3

N-{(E)-3-[2-(2-NAPHTHYLMETHYL)PHENYL]-2-PROPENOYL}-2-THIOPHENESULFONAMIDE (4)

Step 1: Ethyl (E)-3-[2-(2-naphthylmethyl)phenyl]-2-propenoate

The benzyl bromide (500 mg) of example 1, step 2 was treated with 2-naphthylboronic acid according to the same procedure previously described to yield 360 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t), 4.27(2H, q), 4.33 (2H, s), 6.48 (1H, d), 7.2-7.4 (4H, m), 7.45 (2H, m), 7.55 (1H, s), 7.62 (1H, d), 7.8 (3H, m) and 8.15 (1H, d).

Step 2: (E)-3-[2-(2-naphthylmethyl)phenyl]-2-propenoic acid

The hydrolysis of the previous ester (300 mg) was done according to Step 4 of example 1 to yield 202 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.29 (2H, s), 6.32 (1H, d), 7.2-7.4 (6H, m), 7.5 (1H, s), 7.62 (1H, d), 7.73 (3H, m) and 8.19 (1H, d).

Step3: N-{(E)-3-[2-(2-naphthylmethyl)phenyl]-2-propenoyl}-2-thiophenesulfonamide (4)

The coupling reaction of the previous acid (100 mg; 0.35 mmol) was done according to step 5 of example 1 to yield 60 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.24 (2H, s), 6.31 (1H, d), 7.02 (1H, m), 7.15-7.8 (12H, m), 7.84 (1H, m) and 8.08 (1H, d).

The acid was converted to the sodium salt with 1 equivalent of NaOH.

Elemental analysis calcd. for $C_{24}H_{18}NNaO3S_2.H_2O$: C, 60.87; H, 4.22; N, 2.96; S, 13.54; Found: C, 60.36; H, 4.25; N, 3.29; S, 12.53.

EXAMPLE 4

N-[(E)-3-[2-(3,4-DICHLOROBENZYL)PHENYL]-2-PROPENOYL}-2-THIOPHENESULFONAMIDE (8)

Step 1: Ethyl (E)-3-[2-(3,4-dichlorobenzyl)phenyl]-2-propenoate

The benzyl bromide (500 mg) of example 1, step 2 was treated with 3,4-dichlorobenzeneboronic acid according to the same procedure described in step 3 of example 1 to yield 410 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t), 4.03 (2H, s), 4.23 (2H, q), 6.28 (1H, d), 6.90 (1H, dd), 7.1-7.4 (5H, m), 7.57 (1H, d) and 7.89 (1H, d).

Step 2: (E)-3-[2-(3,4-dichlorobenzyl)phenyl]-2-propenoic acid

The hydrolysis of the previous ester (400 mg) was done according to Step 4 of example 1 to yield 296 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.07 (2H, s), 6.31 (1H, d), 6.93 (1H, dd), 7.1-7.4 (5H, m), 7.50 (1H, d) and 7.99 (1H, d).

Step 3: N-[(E)-3-[2-(3,4-dichlorobenzyl)phenyl]-2-propenoyl]-2-thiophenesulfonamide (8)

The coupling reaction of the previous acid (170 mg; 0.55 mmol) was done according to step 5 of example 1 to yield 110 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.07 (2H, s), 6.33 (1H, d), 6.85 (1H, d), 7.07 (3H, m), 7.24 (2H, m), 7.32 (1H, t), 7.53 (1H, d), 7.63 (1H, d), 7.88 (1H, d) and 7.97 (1H, d).

The acid was converted to the sodium salt with 1 equivalent of NaOH.

Elemental analysis calcd. for $C_{20}H_{14}Cl_2NNaO_3S_2.1/2H_2O$: C, 49.7; H, 3.1; N, 2.9; S, 13.27; Found: : C, 49.46; H, 2.9; N, 2.86; S, 13.73;

EXAMPLE 5

N-((E)-3-{2-[(2-NAPHTHYLOXY)METHYL]PHENYL}-2-PROPENOYL)-2-THIOPHENESULFONAMIDE (20)

Step 1: Ethyl (E)-3-{2-[naphthyloxy)methyl]phenyl}-2-propenoate

The benzyl bromide (250 mg, 0.93 mmol) of step 2 in example 1 and 2-naphthol (147 mg) in 5 mL of DMF were treated with cesium carbonate (394 mg) at 40 °C for 12 h. The mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent removed. Purification by silica gel chromatography (10% EtOAc in hexane) yielded 245 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.2 (3H, t), 4.22 (2H, q), 5.28 (2H, s), 6.41 (1H, d), 7.22 (2H, m), 7.3-7.5 (4H, m), 7.55 (1H, m), 7.64 (1H, m), 7.75 (3H, m) and 8.05 (1H, d).

Step 2: (E)-3-{2-[naphthyloxy)methyl]phenyl}-2-propenoic acid

Hydrolysis of the previous ester (245 mg, 0.74 mmol) was done according to step 4 of example 1 to yield 185 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 5.27 (2H, s), 6.45 (1H, d), 7.15-7.25 (2H, m), 7.32 (1H, t), 7.42 (3H, m), 7.55 (1H, d), 7.67 (1H, d), 7.77 (3H, m) and 8.11 (1H, d).

Step 3: N-((E)-3-{2-[(2-naphthyloxy)methyl]phenyl}-2-propenoyl)-2-thiophenesulfonamide (20)

The coupling reaction of the previous acid (150 mg; 0.49 mmol) was done according to step 5 of example 1 to yield 77 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 5.2 (2H, s), 6.39 (1H, d), 7.02 (1H, s), 7.1-7.2 (2H, m), 7.3-7.4 (4H, m), 7.53 (3H, m), 7.71 (3H, m), 7.83 (1H, s) and 8.07 (1H, d).

The product was converted to the sodium salt with 1 equivalent of NaOH.

Elemental analysis calcd. for $C_{24}H_{28}NNaO_4S_2.3/2H_2O$: C, 57.82; H,4.21; N, 2.81; Found: : C, 58.31; H, 3.96; N, 2.91.

EXAMPLE 6

N-{(E)-3-[2-(2-NAPHTHYLSULFINYL)PHENYL]-2-PROPENOYL}-2-THIOPHENESULFONAMIDE (21)

Step 1: 2-(2-naphthylthio)benzaldehyde

A mixture of 2-thionaphthol (5.29 g; 33 mmol), 2-fluorobenzaldehyde (3.73 g; 33 mmol) and potassium carbonate (4.57 g; 33 mmol) in 28 mL of iso-propanol was heated to reflux for 12 h. The mixture was cooled to r.t., diluted with water and filtered. The solution was diluted with EtOAc and washed with water, brine and dry over $MgSO_4$. The crude product (7.9 g) was used as is for the next step.

^{1}H NMR ($CDCl_3$) δ 7.07 (1H, d), 7.32 (2H, m), 7.42 (1H, d), 7.51 (2H, m), 7.78 (1H, m), 7.83 (2H, d), 7.88 (1H, s), 7.95 (1H, s) and 10.39 (1H, s).

Step 2: Ethyl (E)-3-[2-(2-naphthylthio)phenyl]-2-propenoate

The previous aldehyde (7.72 g; 29.2 mmol) was converted to the ethyl ester according to step 1 of example 1 to furnish 6.36 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t), 4.21 (2H, q), 6.36 (1H, d), 7.28 (4H, m), 7.42 (2H, m), 7.61 (1H, d), 7.72 (4H, m) and 8.28 (1H, d).

Step 3: Ethyl (E)-3-[2-(2-naphthylsulfinyl)phenyl]-2-propenoate

The previous ester (3.00 g; 8.97 mmol) in 45 mL of dichloromethane was treated with 1.1 equivalent of mCPBA at 0 °C for 1 h. The mixture was quenched with sodium thiosulfite and extracted with EtOAc. The organic phase was dry over Na_2SO_4 and the crude purified by silica gel chromatography (30% EtOAc in hexane) to yield 2.35 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t), 4.27 (2H, q), 6.26 (1H, d), 7.42 (2H, m), 7.53 (4H, m), 7.77 (2H, m), 7.88 (2H, m), 8.07 (2H, d), 8.22 (1H, s) and 8.28 (2H, m).

Step 4: Ethyl (E)-3-[2-(2-naphthylsulfinyl)phenyl]-2-propenoic acid

The previous ester (1.20 g; 3.43mmol) was hydrolyzed according to the procedure of step 4 of example 1 to yield 1.08 g of the title compound.

^{1}H NMR (methanol-d_6) δ 6.23 (1H, d), 7.33 (1H, dd), 7.45 (3H, m), 7.53 (1H, t), 7.62 (1H, d), 7.8 (3H, m), 7.98 (1H, d), 8.05 (1H, d) and 8.27 (1H, s).

Step 5: 2-{(E)-3-[2-(2-naphthylsulfinyl)phenyl]-2-propenoyl}-2-thiophenesulfonamide (21)

The coupling reaction of the previous acid (500 mg; 1.55 mmol) was done according to step 5 of example 1 to yield 416 mg of the title compound.

^{1}H NMR (methanol-d_6) δ 6.19 (1H, d), 7.1 (1H, m), 7.22 (1H, dd), 7.45 (3H, m), 7.55 (2H, m), 7.67 (1H, d), 7.72-7.85 (4H, m), 7.99 (1H, d), 8.1 (1H, d) and 8.17 (1H, s).

The sodium salt was prepared with 1N NaOH. Elemental analysis calcd. for $C_{23}H_{16}NNaO_4S_3.1/2H_2O$: C, 55.36; H,3.40; N, 2.81; S, 19.27; Found: : C,55.00; H, 3.62; N, 2.81; S, 18.18.

EXAMPLE 7

N-{(E)-3-[2-(2-NAPHTHYLOXY)PHENYL]-2-PROPENOYL}-2-THIOPHENESULFONAMIDE (28)

Step 1: Ethyl (E)-3-[2-(2-naphthyloxy)phenyl]-2-propenoate

2-fluoro benzaldehyde (3.0 g; 24.2 mmol), 2-naphthol (24.2 mmol) and potassium carbonate (26.6 mmol) were heated at reflux in dimethyl acetamide for 2 h. The mixture was cooled to r.t., diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent removed. Purification by silica gel chromatography (10% EtOAc in hexane) yielded 3.4 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 6.93 (1H, d), 7.17-7.23 (1H, m), 7.28 (1H, dd), 7.37 (1H, s), 7.37 (3H, m), 7.7 (1H, d), 7.84 (2H, m), 7.94 (1H, d) and 10.53 (1H, s).

Step 2: Ethyl (E)-3-[2-(2-naphthyloxy)phenyl]-2-propenoate

The previous aldehyde (2.00 g; 8.0 mmol) was converted to the title compound according to step 1 of example 1 to yield 2.52 g .

^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t), 4.21 (2H, q), 6.55 (1H, d), 6.9 (1H, d), 7.15 (1H, t), 7.25 (3H, m), 7.42 (2H, m), 7.65 (2H, m), 7.83 (2H, t) and 8.02 (1H, d).

Step 3: (E)-3-[2-(2-naphthyloxy)phenyl]-2-propenoic acid

The previous ester (2.52 g; 7.9 mmol) was hydrolyzed according to the procedure of step 4 of example 1 to yield 1.57 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 6.62 (1H, d), 7.03 (1H, d), 7.2-7.5 (6H, m), 7.78 (1H, d) and 7.88-8.03 (4H, m). HRMS calcd. for $C_{19}H_{14}O_3 + H^+$ = 291.1021; Found: 291.1022.

Step 4: N-[(E)-3-[2-(2-naphthyloxy)phenyl]-2-propenoyl]-2-thiophenesulfonamide (28)

The coupling reaction of the previous acid (1.00 g; 3.4 mmol) was done according to step 5 of example 1 to yield 790 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 6.91 (1H, d), 6.97 (1H, d), 7.15(1H, dd), 7.24 (1H, t), 7.29 1H, dd), 7.37 (1H, d), 7.40-7.55 (3H, m), 7.74-7.83 (2H, m), 7.92 (2H, m) and 7.99 (2H, m).

The sodium salt was prepared with 1N NaOH. HRMS calcd. for $C_{23}H_{16}NNaO_4S_2 + H^+$ = 458.0497; Found:458.0497.

EXAMPLE 8
THIOPHENE-2-SULFONYL CARBAMIC ACID [2-(2-NAPHTHYLSULFONYL)PHENYL]METHYL ESTER (31)

Step 1: [2-(2-naphthylthio)phenyl]methanol

To 2-(2-naphthylthio) benzaldehyde (7.24 g; 27.4 mmol from Example 6, step 1) in 70 mL of methanol and 30 mL of THF at 0 °C was added $NaBH_4$ (54.8 mml) portionwise. After 1h at 0 °C, the solution was brought to r.t. and quenched with water. After dilution with EtOAc, the solution was washed with water and brine. The organic phase was dry over Na_2SO_4, filtered and the crude purified by silica gel chromatography to yield 6.71 g of the title compound.

^1H NMR (acetone-d_6) δ 4.29 (1H, t), 4.7 (2H, d), 7.29 (2H, m), 7.35-7.52 (4H, m), 7.71 (2H, m), 7.77 (1H, m) and 7.83 (2H, m).

Step 2: [2-(2-Naphthylsulfonyl)phenyl]methanol

To the previous sulfide (500 mg; 1.88 mmol) in 8 mL of dichloromethane at 0 °C was added m-CPBA (5.64 mmol) and let stirred for 2 h. The mixture was diluted with EtOAc and washed with NaOH (1N) and brine. The organic phase was dry over Na_2SO_4, filtered and the crude purified by silica gel chromatography (40% EtOAc in hexane) to yield 390 mg of the title compound.

^1H NMR (acetone-d_6) δ 4.37 (1H, t), 4,9 (2H, d), 7.57 (1H, dt), 7.65-7.80 (4H, m), 7.82 (1H, d), 8.0-8.1 (2H, m), 8.2 (2H, m) and 8.63 (1H, s).

Step 3: 2-Thiophenesulfonyl isocyanate

A mixture of 2-thiophenesulfonylamide (1.5 g) and oxalyl chloride (6 mL) in 10 mL of 1,2-dichloroethane was refluxed for 14h. The solvent was removed under vacuum and the crude used as is for the next step.

Step 4:

To the alcohol of step 2 (250 mg; 0.84 mmol) in ether at 0 °C was added the previous isocyanate (2 equivalent) and let stirred 1h at 0 °C. The solution was quenched with water and extracted with EtOAc. The organic phase dry over Na_2SO_4, filtered and the crude purified by silica gel chromatography (5% CH_3OH in CH_2Cl_2) to yield 300 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 5.55 (2H, s), 7.08 (1H, m), 7.55-7.72 (6H, m), 7.82 (2H, m), 8.0 (1H, d), 8.07 (1H, d), 8.2 (2H, m) and 8.66 (1H, s).

The sodium salt was prepared with 1N NaOH.

Elemental analysis calcd. for $C_{22}H_{16}NNaO_6S_3.2H_2O$: C, 48.44; H,3.67; N, 2.57; S, 17.63;

Found: : C,48.86; H, 3.13; N, 2.63; S, 16.46.

EXAMPLE 9

N-({2-[2-(2-NAPHTHYLMETHYL)PHENYL]CYCLOPROPYL} CARBONYL-2-THIOPHENESULFONAMIDE (45)

Step 1: Ethyl 2-[2-(2-naphthylmethyl)phenyl]-1-cyclopropanecarboxylate

The ethyl ester (300 mg; 0.95 mmol) of step 1 in example 3 and $Pd(OAc)_2$ (10 mg) were treated with diazomethane at 0° C for 1h. The solvent was removed and the crude oil purified by silica gel chromatography (5% EtOAc in hexane) to yield 300 mg of the title compound.

^1H NMR ($CDCl_3$) δ 1.1 (3H, t), 1.27 (1H, m), 1.45 (1H, m), 1.7 (1H, m), 2.53 (1H, m), 3.98 (2H, m), 4.29 (2H, s), 7.0 (1H, m), 7.18 (3H, m), 7.27 (1H, m), 7.39 (2H, m), 7.48 (1H, s) and 7.75 (3H, m).

Step 2: 2-[2-(2-naphthylmethyl)phenyl]-1-cyclopropanecarboxylic acid

The previous ester (300 mg; 0.91 mmol) was hydrolyzed according to the procedure of step 4 of example 1 to yield 230 mg of the title compound.

^1H NMR ($CDCl_3$) δ 1.45 (1H, m), 1.6 (1H, m), 1.8 (1H, m), 2.67 (1H, m), 4.33 (2H, s), 7.1 (1H, m), 7.24 (4H, m), 7.41 (2H, m), 7.58 (1H, s) and 7.78 (3H, m).

Step 3: N-({2-[2-(2-naphthylmethyl)phenyl]cyclopropyl}carbonyl-2-thiophenesulfonamide (45)

The coupling reaction of the previous acid (230 mg; 0.76 mmol) was done according to step 5 of example 1 to yield 100 mg of the title compound.

^1H NMR ($CDCl_3$) δ 1.32 (1H, m), 1.48 (1H, m), 1.63 (1H, m), 2.6 (1H, m), 4.13 (2H, s), 6.97 (2H, m), 7.12 (4H, m), 7.38 (3H, m), 7.52 (1H, d), 7.65 (2H, m) and 7.79 (2H, m). The sodium salt was prepared with 1N NaOH. Elemental analysis calcd. for $C_{25}H_{20}NNaO_3S_2.1/2H_2O$: C, 62.75; H, 4.39; N, 2.93; S, 13.4; Found: : C,62.25; H, 4.24; N, 3.02; S, 12.15.

EXAMPLE 10

N-((E)-3-(2-(6-BENZYLOXY-2-NAPHTHYL)METHYL)PHENYL)-2-PROPENOYL)-5-BROMO-2-METHOXYBENZENESULFONAMIDE (46)

(E)-3-(2-(6-benzyloxy-2-naphthyl)methyl)phenyl)-2-propenoic acid

Step 1: [(6-bromo-2-naphthyl)oxy](phenyl)methane

To a mixture of 6-bromo-2-naphthol (1.99 g, 8.9 mmol) and benzyl bromide (1.2 ml, 1.1 equiv.) in DMF (18 ml) at 0°C was added a suspension of NaH 80% in oil (324 mg, 1.2 equiv.) and the mixture was stirred at 0°C for an hour and at r.t. for another hour. After addition of half saturated NH_4Cl, the product was extracted in i-PrOAc, washed with 1 N HCl, dried over Na_2SO_4 and concentrated to yield 2.84 g of an oil.

Step 2: 6-benzyloxy-2-naphthaleneboronic acid

To a solution of the previous bromide (940 mg, 3.00 mmol) in THF (15 ml) at -78°C was added n-BuLi 1.6 M in hexanes (2.2 ml, 1.2 equiv.) and the mixture was stirred at -78°C for 15 min. Tri-isopropyl borate (0.97 ml, 1.4 equiv.) was added and the reaction mixture was warmed to r.t. After addition of 2 N HCl, the product was extracted in EtOAc, dried over Na_2SO_4 and concentrated to yield a solid. This solid was washed with ether:hexane 1:1 to yield 679 mg of pure material.

^1H NMR (Acetone-d_6:DMSO-d_6) δ 5.27 (2H, s), 7.22 (1H, dd), 7.33 (1H, dd), 7.40 (3H, m), 7.54 (2H, d), 7.63 (2H, s), 7.72 (1H, d), 7.83 (1H, d), 7.90 (1H, d), 8.36 (1H, s).

Step 3: Ethyl (E)-3-(2-{[6-benzyloxy)-2-naphthyl]methyl}phenyl)-2-propenoate

A mixture of the previous boronic acid (1.05 g, 3.8 mmol), $Pd(Ph_3P)_4$ (185 mg), the benzylic bromide of step 2 in example 1 (1.07 g, 4.0 mmol), 2 M aq. Na_2CO_3 (4 ml) and toluene (8 ml) was degazed and stirred at 100° C under nitrogen for 4 h. After addition of half saturated NH_4Cl, the product was extracted in EtOAc, dried over Na_2SO_4 and concentrated. Purification by flash chromatography with EtOAc:toluene:hexane 2.5:75:25 yielded 1.17 g of the title compound as an oil.

Step 4: (E)-3-(2-{[6-(benzyloxy)-2-naphthyl]methyl}phenyl)-2-propenoic acid

The previous ester was hydrolyzed according to the procedure of step 4 of example 1 to yield the title compound.

Step 5: 5-Bromo-2-methoxybenzenesulfonamide

To 5-bromo-2-methoxybenzenesulfonyl chloride (45g; 157.6 mmol, from Lancaster Chemical) at 0°C in THF , was added concentrated NH_4OH (42.5 mL) and the reaction mixture was brought to r.t. for 2 h. The reaction mixture was diluted with EtOAc, extracted with $NaHCO_3$ (2X), brine, and the organic phase was dried over $MgSO_4$. The solvent was removed to give the title compound.

Step 6: N-((E)-3-(2-(6-benzyloxy-2-naphthyl)methyl)phenyl)-2-propenoyl)-5-bromo-2-methoxybenzenesulfonamide (46)

To the acid from step 5 (190 mg, 0.482 mmol) in CH_2Cl_2 was added DMF (10 µL) and oxalyl chloride (60 µL) at 0° C and the mixture was warmed to r.t. for an hour and concentrated to dryness. The resulting acid chloride was redissolved in CH_2Cl_2:THF 1:1 (10 mL) and 5-bromo-2-methoxybenzenesulfonamide (154 mg, 1.2 equiv., from step 6) and Et_3N (135 µL, 2 equiv.) were added at 0°C. The mixture was then warmed to r.t. for an hour, 0.5 N HCl was added and the product was extracted in i-PrOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene:acetic acid 20:80:1 to yield 93 mg of a white solid.

^1H NMR ($CDCl_3$) δ

MS (APCI, neg.) 643.3, 641.8, 640.0 (M-1), 393.2.

EXAMPLE 11

N-{(E)-3-[2-NAPHTHYLMETHYL)PHENYL)]-2-PROPENOYL}-5-BROMO-2-METHOXY-1-BENZENESULFONAMIDE (301)

Step 1: N-{(E)-3-[2-naphthylmethyl)phenyl)]-2-propenoyl}-5-bromo-2-methoxy-1-benzenesulfonamide (301)

The carboxylic acid (400 mg; 1.22 mmol) of example 3 step 2 was coupled with 5-bromo-2-methoxy-1-benzenesulfonyl chloride according to the procedure of step 5 in example 1 to yield 284 mg of the title compound.

^{1}H NMR (acetone-d_6-DMSO-d_6) δ 3.85 (3H, s), 4.31 (2H, s), 6.65 (1H, d), 7.15 (1H, d), 7.3 (1H, m), 7.35-7.50 (4H, m), 7.55-7.65 (2H, m), 7.7-7.9 (5H, m) and 8.01 (1H, d).

The acid was converted to the sodium salt with 1 equivalent of NaOH. Elemental analysis calcd. for $C_{27}H_{21}BrNNaO_4S.1/2H_2O$: C, 57.15; H,3.88; N, 2.47; Found: : C, 56.88; H, 3.73; N, 2.52.

EXAMPLE 12

N-[(E)-3-[5-CHLORO-2-(2-NAPHTHYLMETHYL)PHENYL]-2-PROPENOYL]-2-THIOPHENESULFONAMIDE (303)

Step 1: 5-chloro-2-methylbenzaldehyde

To a solution of 2-bromo-4-chlorotoluene (20.0 g; 97.3 mmol) in 300 mL of THF at -78 °C was added dropwise a 2.5 M solution of n-BuLi (102.2 mmol). After 30 min of stirring at that temperature, 1-formylpiperidine (11.4 mL) in 10 mL of THF was added and the solution left for 1 h. It was brought to 0 °C , quenched with NH_4OAc (25%) and diluted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and the solvent removed to yield 13.3 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 2.6 (3H, s), 7.15 (1H, d), 7.4 (1H, d), 7.75 (1H, s) and 10.2 (1H, s).

Step 2: Ethyl (E)-3-(5-chloro-2-methylphenyl)-2-propenoate

The previous aldehyde (13.3 g; 86.0 mmol) was converted to the ethyl cinnamate according to step 1 of example 1 to yield 16.67 g.

^{1}H NMR ($CDCl_3$) δ 1.2 (3H, t), 2.26 (3H, s), 4.15 (2H, q), 6.21 (1H, d), 6.99 (1H, d), 7.13 (2H, m), 7.39 (1H, s) and 7.73 (1H, d).

Step 3: Ethyl (E)-3-[2-(bromomethyl)-5-chlorophenyl]-2-propenoate

The previous ester (16.66 g; 74.1 mmol) was converted to the benzylic bromide according to step 2 of example 1 to yield 9.0 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 1,2 (3H, t), 4.25 (2H, q), 4.5 (2H, s), 6.4 (1H, d), 7.28 (2H, s), 7.55 (1H, s) and 7.95 (1H, d).

Step 4: Ethyl (E)-3-[5-chloro-2-(2-naphthylmethyl)phenyl]-2-propenoate

The previous benzylic bromide was coupled in a Suzuki type reaction with 2-naphthylboronic acid according to step 3 of example 1 to yield 1.14 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t), 4.09 (2H, q), 4.12 (2H, s), 6.2 (1H, d), 7.03 (1H, d), 7.15 (2H, m), 7.3 (2H, m), 7.37 (1H, s), 7.45 (1H, s), 7.65 (3H, m) and 7.87 (1H, d).

Step 5: (E)-3-[5-chloro-2-(2-naphthylmethyl)phenyl]-2-propenoic acid

The hydrolysis of the previous ester (1.14 g) was done according to Step 4 of example 1 to yield 0.99 g of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.23 (2H, s), 6.31 (1H, d), 7.12 (1H, d), 7.22 (1H, m), 7.3 (1H, m), 7.42 (2H, m), 7.48 (1H, s), 7.59 (1H, s), 7.75 (3H, m) and 8.05 (1H, d).

Step 6: N-{(E)-3-[5-chloro-2-(2-naphthylmethyl)phenyl]-2-propenoyl}-2-thiophenesulfonamide (303)

The coupling reaction of the previous acid (400 mg; 1.22 mmol) was done according to step 5 of example 1 to yield 272 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 4.25 (2H, s), 6.58 (1H, d), 7.0 (1H, t), 7.23 (2H, m), 7.33 (1H, m), 7.39 (2H, m), 7.5-7.6 (2H, m), 7.55 (5H, m) 7.86 (1H, m) and 8.04 (1H, d).

The product was converted to the sodium salt with 1 equivalent of NaOH. Elemental analysis calcd. for $C_{24}H_{17}ClNNaO_3S_2.1/2H_2O$: C, 57.76; H,3.64; N, 2.81; S, 12.84; Found: : C, 57.78; H, 3.62; N, 2.86; S, 12.85.

EXAMPLE 13

(E)-3-{4-CHLORO-2-[6-FLUORO-2-NAPHTHYL)METHYL]PHENYL}-2-PROPENOIC ACID SODIUM SALT (457)

Step 1: Ethyl (E)-3-(5-chloro-2-methylphenyl)-2-propenoate

To 2-bromo-4-chloro toluene (20.0g; 97.3 mmol) in 300 mL of THF at -78 oC was added n-BuLi 2.5 M (40.8 mL) dropwise. After 20 min. 1-formylpiperidine (11.4 mL; 103.0 mmol) in 10 mL of THF was added dropwise. After 30 min the reaction mixture was brought to 0°C and quenched with HCl (10%) and diluted with EtOAc. The organic phase was collected, dry and the solvent evaporated to yield 13.3g (89%) of 5-chloro-2-methylbenzaldehyde. This crude aldehyde was mixed with 1.1 equivalent of triethyl phosphonoacetate in THF. Sodium hydride 80% (1.3 equivalent) was added portionwise and 1 h later the reaction was quenched with 25% NH4Cl. The reaction mixture was diluted with EtOAc and the organic phase collected, dried and the solvent removed. The crude oil was purified on a short pad of silica gel using 5% EtOAc in hexane to afford 16.67 g of the title compound.

Alternatively, this procedure can be done in one reaction vessel. At the end of the first step, the flask is brought to rt and the phosphonoacetate in THF is added.

1H NMR (CDCl3) δ 1.21 (3H, t), 2.27 (3H, s), 4.15 (2H, q), 6.22 (1H, d), 6.95-7.15 (3H, m), 7.40 (1H, s) and 7.75 (1H, d).

Step 2: Ethyl(E)-3-[2-(bromomethyl)-5-chlorophenyll-2-propenoate

The bromination was done according to step 2 of example 1 to provide the title compound in 45% yield.

^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t), 4.27 (2H, q), 4.52 (2H, s), 6.43 (1H, d), 7.30 (2H, s), 7.55 (1H, s) and 7.93 (2H, d).

Step 3: 6-Fluoro-2-naphthol

A solution of 2-(4-fluorophenyl)acetyl chloride (5.0g; 29 mmol) in CH_2Cl_2 was added to $AlCl_3$ (7.73g;58 mmol) in CH_2Cl_2 at -20 ^{0}C over 30 min. Trimethylsilyl acetylene (9.96g; 101.43 mmol) was added also over 30 min and stirred at -10 ^{0}C for 1h. The mixture was poured in

ice and extracted with EtOAc. The organic phase was washed with water, $NaHCO_3$ and brine. After purification by gel silica chromatography (10% EtOAc in hexane) 2.43 g (36%) of 3-(trimethylsilyl)-6-chloro-2-naphthol was collected. The desylilation was done with TFA in CH_2Cl_2 at rt overnight. Purification by gel silica chromatography (10% EtOAc in hexane) afforded the title compound in 69% yield.

^{1}H NMR ($CDCl_3$) δ 7.10-7.20 (3H, m), 7.37 (1H, dd) and 7.65 (2H, m).

Step 4: Ethyl (E)-3-[4-chloro-2-[(6fluoro-2-naphthyl)methyl]phenyl]-2-propenoate

The naphthol of Step 3 was converted to the triflate with triflic anhydride/pyridine in CH_2Cl_2 at 0 °C. This was coupled with the organozinc of the benzyl bromide of step 2 in example 13, with dppf and $Pd(dba)_2$. This yielded the title compound in 47% yield after purification by silica gel chromatography (10% EtOAc in hexane).

^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t), 4.20 (2H, q), 6.30 (1H, d), 7.10-7.27 (4H, m), 7.38 (1H, dd), 7.48 (1H, s), 7.57 (1H, dd), 7.66 (2H, m) and 7.95 (1H, d).

Step 5: (E)-3-[4-Chloro-2-[(6-fluoro-2-naphthyl)methyl]phenyl]-2-propenoic acid, sodium salt

The hydrolysis of the ester of Step 4 (1.03g; 2.7 mmol) was done according to step 4 of example 1 to yield 800mg (87%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (CDCl3) δ 4.21 (2H, s), 6.30 (1H, d), 7.10-7.40 (4H, m), 7.38 (1H, dd), 7.45 (1H, s), 7.58 (1H, d), 7.68 (2H, m) and 8.05 (1H, d).

LRMS for M-1= 339.

EXAMPLE 14

5-BROMO-N((E)-3-[5-CHLORO-2-[(6-FLUORO-2-NAPHTHYL-2)METHYL]PHENYL]-2-PROPENOYL)-2-METHOXYBENZENESULFONAMIDE SODIUM SALT (378)

Step 1: 5-Bromo -N-((E)-3-{5-chloro-2-[(6-fluoro-2-naphthyl)methyl]phenyl}-2-propenoyl)-2-methoxybenzenesulfonamide

The coupling reaction of the acid of Example 1 Step 5 with 5-bromo-2-methoxybenzesulfonamide (500 mg; 1.47 mmol) was done according to step 5 of example 1 to yield 662 mg (77%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (DMSO-d6) δ 3.78 (3H, s), 4.22 (2H, s), 6.53 (1H, d), 7.17 (1H, d), 7.27 (1H, d), 7.35 (2H, m), 7.47 (1H, dd), 7.51 (1H, s), 7.58 (1H, d), 7.64 (1H, dd) and 7.75-7.90 (5H, m).

LRMS for M-1= 588.

EXAMPLE 15

(E)-3-{5-CHLORO-2-[(6-CHLORO-2-NAPHTHYL)METHYL]PHENYL}-2-PROPENOIC ACID SODIUM SALT (469)

Step 1: 6-Chloro-2-naphthol

The title compound was prepared from 2-(4-fluorophenyl)acetyl chloride according to step 3 of example 13.

^{1}H NMR ($CDCl_3$) δ 7.10 (2H, m), 7.34 (1H, dd), 7.55-7.67 (2H, m) and 7.72 (1H, s).

Step 2: Ethyl (E)-3-{5-chloro-2-[(6-chloro-2-naphthyl)methyl]phenyl}-2-propenoate

The title compound was prepared according to step 4 of example 13 in 30% yield.

^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t), 4.20 (4H, m), 6.29 (1H, d), 7.10 (1H, d), 7.22 (2H, m), 7.33 (1H, dd), 7.42 (1H, s), 7.53 (1H, d), 7.61 (2H, d), 7.70 (1H, s) and 7.91 (1H, d).

Step 3: (E)-3-{5-Chloro-2-[(6-chloro-2-naphthyl)methyl]phenyl}-2-propenoic acid, sodium salt

The hydrolysis of the ester of Step 2 (620 mg; 1.6 mmol) was done according to step 4 of example 1 to yield 500mg (87%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.22 (2H, s), 6.30 (1H, d), 7.15 (1H, d), 7.20-7.39 (3H, m), 7.43 (1H, s), 7.56 (1H, s), 7.62 (2H, t), 7.75 (1H, s) and 8.02 (1H, d).

Elemental analysis calcd for $C_{20}H_{13}Cl_2NaO_2 .H_2O$: C, 60.48; H, 3.78; Found C, 60.68, H, 3.63.

EXAMPLE 16

5-BROMO-N((E)-3-{5-CHLORO-2-[(6-CHLORO-2-NAPHTHYL-2)METHYL]PHENYL}-2-PROPENOYL)-2-METHOXYBENZENESULFONAMIDE, SODIUM SALT (450)

Step 1: 5-Bromo -N-((E)-3-{5-chloro-2-[(6-chloro-2-naphthyl)methyl]phenyl}-2-propenoyl)-2-methoxybenzenesulfonamide

The coupling reaction of the acid of Example 15 Step 3 (500 mg; 1.4 mmol) was done according to step 5 of example 1 with 5-bromo-2-methoxybenzesulfonamide to yield 662 mg (74%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (DMSO-d6) δ 3.78 (3H, s), 4.22 (2H, s), 6.53 (1H, d), 7.20 (1H, d), 7.30-7.40 (2H, m), 7.45 (2H, m), 7.55 (1H, s), 7.59 (1H, s), 7.79 (3H, m), 7.85-7.92 (2H, m) and 7.98 (1H, d).

Elemental analysis calcd for C27H19BrCl2NNaO4S .2H2O : C, 49.01; H, 3.33; N, 2.14; Found C, 48.89, H, 3.47; N, 2.11.

EXAMPLE 17

(E)-3-(5-CHLORO-2-{[6-DIFLUOROMETHOXY)-2-NAPHTHYL]METHYL}PHENYL-2-PROPENOIC ACID, SODIUM SALT (505)

Step 1: 6-Bromo-2-difluoromethoxynaphthalene

Methyl chlorodifluoroacetate (5.3 mL) was added dropwise to 6-bromonaphthol (10.25 g; 45.9 mmol) and potassium carbonate (7.61g; 55.1 mmol) at 90 0C in 160 mL of DMF for 6 h. Purification by gel silica chromatography (3% EtOAc in hexane) gave 4.80 g (38%) of the title compound.

1H NMR (CDCl3) δ 6.61 (1H, t), 7.31 (1H,dd), 7.48 (1H, d), 7.56 (1H, dd), 7.67 (1H, d), 7.72 (1H, d) and 8.01 (1H, d).

Step 2: Ethyl (E)-3-(5-chloro-2-{[6-difluoromethoxy)-2-naphthyl]methyl}phenyl)-2-propenoate

The corresponding boronic acid of the previous halide was coupled according to step 3 of example 1 of the title compound in 57% yield.

1H NMR (CDCl3) δ 1.25 (3H, t), 4.22 (4H, m), 6.28 (1H, d), 6.53 (1H, t), 7.11 (1H, d), 7.25 (2H, m), 7.45 (2H, d), 7.55 (1H, d), 7.72 (2H, t) and 7.92 (1H, d).

Step 3: (E)-3-(5-Chloro-2-{[6-difluoromethoxy)-2-naphthyl]methyl}phenyl)-2-propenoic acid, sodium salt

The hydrolysis of the ester of Step 2 (1.9 g; 4.7 mmol) was done according to step 4 of example 1 to yield 600mg of the title compound.

1H NMR of sodium salt (DMSO-d6) δ 4.20 (2H, s), 6.29 (1H, d), 7.10-7.40 (6H, m), 7.58 (3H, m) and 8.84 (2H, t).

HRMS calc'd for $C_{21}H_{14}O_3F_2ClNa$ +H= 411.0575; Found: 411.0577.

EXAMPLE 18

5-BROMO-N-[(E)-3-(5-CHLORO-2-{[6-DIFLUOROMETHOXY)-2-NAPHTHYL_METHYL)-2-PROPENOYL]-2-METHOXYBENZENESULFONAMIDE, SODIUM SALT (447)

Step 1: 5-Bromo -N-[(E)-3-(5-chloro-2-{[6-difluoromethoxy)-2-naphthyl]methyl}phenyl)-2-propenoyl]-2-methoxybenzennesulfonamide

The coupling reaction of the acid of Example 17 Step 3 (1.00g; 2.57 mmol) was done according to step 5 of example 1 with 5-bromo-2-methoxybenzesulfonamide to yield 915 mg (56%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR of sodium salt DMSO-d6) δ 3.66 (3H, s), 4.18 (2H, s), 6.36 (1H, d), 6.92 (1H, d), 7.20-7.35 (5H, m), 7.48 (2H, m), 7.55-7.65 (3H, m) and 7.80 (3H, m).

LRMS for M-1= 634.

EXAMPLE 19

(E)-3-[2-(3,4-DICHLOROBENZYL)-5-CHLOROPHENYL]-2-PROPENOIC ACID, SODIUM SALT (535)

Step 1: Ethyl (E)-3-[2-(3,4-dichlorobenzyl)-5-chlorophenyl)-2-propenoate

The benzyl bromide of step 2 of example 13 was treated with 3,4-dichlorobenzeneboronic acid according to the procedure described in step 3 of example 1 to yield the title compound in 67% yield.

1H NMR (CDCl3) δ 1.30 (3H, t), 4.00 (2H, s), 4.23 (2H, q), 6.30 (1H, d), 6.90 (1H,dd), 7.09 (1H, d), 7.15 (1H, s), 7.28 (1H, m), 7.32 (1H, d), 7.55 (1H, d) and 7.79 (1H, d).

Step 2: (E)-3-[2-(3,4-Dichlorobenzyl)-5-chlorophenyl)-2-propenoic acid, sodium salt

The hydrolysis of the ester of Step 1 (1.00 g; 2.7 mmol) was done according to step 4 of example 1 to yield 907 mg (98%) of the title compound.

1H NMR (CDCl3) δ 3.95 (2H, s), 6.30 (1H, d), 6.86 (1H, d), 7.08 (2H, m), 7.32 (2H, m), 7.55 (1H, s) and 7.90 (1H, d).

LRMS for M-1= 339.

EXAMPLE 20

5-BROMO-N-{(E)-3-[5-CHLORO-2-(3,4-DICHLOROBENZYL)PHENYL]-2-PROPENOYL}-2-METHOXYBEZENESULFONAMIDE, SODIUM SALT (421)

Step 1: 5-Bromo-N-{(E)-3-[5-chloro-2-)3,4-dichlorobenzyl)phenyll-2-propenoyl}-2-methoxybenzenesulfonamide

The coupling reaction of the acid of Example 19 Step 2 (0.600 g; 1.75 mmol) was done according to step 5 of example 1 with 5-bromo-2-methoxybenzesulfonamide to yield 548 mg (53%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (DMSO-d6) δ 3.85 (3H, s), 4.10 (2H, s), 6.54 (1H, s), 7.01 (1H, d), 7.22 (1H, d), 7.32 (2H, m), 7.40-7.50 (2H, m), 7.56 (1H, s), 7.67 (1H, d), 7.86 (1H, d), 7.91 (1H, s) and 12.37 (1J, s).

LRMS for M-1= 586.

EXAMPLE 21

5-BROMO-N-{(E)-3-[4-CHLORO-2-(2-NAPHTHYLMETHYL)PHENYL]-2-PROPENOYL}-2-METHOXYBENZENESULFONAMIDE, SODIUM SALT (449)

Step 1: Ethyl (E)-3-{4-chloro-2-[(2-naphthylmethyl)phenyl]-2-propenoate

2-Bromo-5-chloro toluene (20.0 g) was converted to the corresponding aldehyde and then to the cinnamate according to step 1 of example 13. This cinnamate was converted to the benzylic bromide according to step 2 of example 1 and coupled via a Suzuki coupling reaction according to step 3 of example 1 with naphthalene boronic acid to yield the title compound.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t), 4.22 (4H, m), 6.29 (1H, d), 7.15-7.27 (3H, m), 7.42 (2H, m), 7.52 (2H, m), 7.75 (3H, m) and 7.99 (1H, d).

Step 2: (E)-3-{4-Chloro-2-[(2-naphthylmethyl)phenyl]-2-propenoic acid (530)

The hydrolysis of the ester of Step 1 (0.56 g; 1.57 mmol) was done according to step 4 of example 1 to yield 450 mg (88%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.24 (2H, s), 6.30 (1H, d), 7.20-7.30 (3H, m), 7.42 (2H, m), 7.51 (2H, m), 7.75 (3H, m) and 8.09 (1H, d).

LRMS for M-1= 321.

Step 3: 5-Bromo-N-{[(E)-3-[4-chloro-2-(2-naphthylmethyl)phenyl]propenoyl}-2-methoxybenzenesulfonamide

The coupling reaction of the acid of Step 2 (0.296 g; 0.89 mmol) was done according to step 5 of example 1 with 5-bromo-2-methoxybenzesulfonamide to yield 213 mg (42%) of the title compound. The sodium salt was prepared with 1N NaOH.

^{1}H NMR (ACETONE-MEOH-d_6) δ 3.70 (3H, s), 4.20 (2H, s), 6.44 (1H, d), 6.95 (2H, m), 7.25 (3H, m), 7.40 (2H, m), 7.55 (3H, m), 7.75 (3H, m), 7.95 (1H, d) and 8.02 (1H, d).

LRMS for M-1= 568.

EXAMPLE 22

(E)-3-[5-METHOXY-2-(2-NAPHTHMETHYL)PHENYL]-2-PROPENOIC ACID, SODIUM SALT (534)

Step 1: (2-Bromo-4-methoxyphenyl)(2-naphthyl)methanone

$AlCl_3$ (17.48 g; 131.1 mmol) was added portionwise to a mixture of 3-bromocresol (16.04 g; 87.4 mmol) and 2-naphthoyl chloride (25.00 g; 131.1 mmol) in 50 mL of $CHCl_3$ gave 14.0 g (47%) of the title compound.

1H NMR ($CDCl_3$) δ 3.78 (3H, s), 6.92 (1H, dd), 7.19 (1H, d), 7.38 (1H, d), 7.50 (1H, t), 7.59 (1H, t), 7.89 (3H, m), 7.95 (1H, dd) and 8.18 (1H, s).

Step 2: 2-(2-Bromo-4-methoxybenzyl)naphtalene

To the methanone of Step 1 (14.0 g) and triethylsilane (15 mL) in 15 mL of $CHCl_3$ was added TFA and was heated to 50°C overnight. The solution was cooled and quenched with NaOH (2N) to provide the title compound in 82% yield.

1H NMR ($CDCl_3$) δ 3.75 (3H, s), 4.20 (2H, s), 6.75 (1H, dd), 7.07 (1H, d), 7.12 (1H, s), 7.30 (1H, d), 7.42 (2H, m), 7.58 (1H, s) and 7.76 (3H, m).

Step 3: Ethyl (E)-3-[5-methoxy-2-(2-naphthylmethyl)phenyl]-2-propenoate

The naphthalene of Step 2 was converted to the corresponding aldehyde according to the step 1 of example 13 in 98% yield. This aldehyde was then converted to the cinnamate according to step 1 of example 13 in 90% yield.

1H NMR ($CDCl_3$) δ 3.70 (3H, s), 4.11 (4H, m), 6.20 (1H, d), 6.77 (1H, dd), 6.99 (1H, d), 7.03 (1H, d), 7.15 (1H, d), 7.30 (2H, m), 7.39 (1H, s), 7.60-7.70 (3H, m) and 7.90 (1H, s).

Step 4: (E)-3-[5-Methoxy-2-(2-naphthmethyl)phenyl]-2-propenoic acid

The hydrolysis of the ester of Step 3 (2.83 g; 8.2 mmol) was done according to step 4 of example 1 to yield 2.16 g (83%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (CDCl3) δ 3.70 (3H, s), 4.13 (2H, s), 6.20 (1H, d), 6.80 (1H, dd), 7.02 (2H, m), 7.15 (1H, d), 7.29 (2H, m), 7.39 (1H, s), 7.62 (3H, m) and 8.03 (1H, d).

LRMS calcd for M-1= 317.

EXAMPLE 23

5-BROMO-2-METHOXY-N-{(E)-3-[5-METHOXY-2-(2-NAPHTHYLMETHYL)PHENYL]-2-PROPENOYL}BENZENESULFONAMIDE SODIUM SALT (448)

Step 1: 5-Bromo-2-methoxy-N-{(E)-3-[5-methoxy-2-(2-naphthylmethyl)phenyl]-2-propenoyl}benzenesulfonamide

The coupling reaction of the acid of Example 22 Step 4 (0.600 g; 1.88 mmol) was done according to step 5 of example 1 with 5-bromo-2-methoxybenzesulfonamide to yield 573 mg (57%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (CDCl3) δ 3.72 (3H, s), 3.77 (3H, s), 4.13 (2H, s), 6.40 (1H, d), 6.70 (1H, d), 6.85 (1H, dd), 7.02 (1H, d), 7.10-7.20 (2H, m), 7.37 (3H, m), 7.57 (1H, dd), 7.60-7.80 (3H, m),7.95 (1H, d), 8.15 (1H, d) and 9.12 (1H, broad s).

LRMS calcd for M-1= 564.

EXAMPLE 24

(E)-3-[5-CHLORO-2-(4-CHLOROBENZYL)PHENYL]-2-PROPENOIC ACID SODIUM SALT (537)

Step 1: Ethyl(E)-3-[5-chloro-2-(4-chlorobenzyl)phenyl]-2-propenoate

The benzyl bromide of step 2 of example 13 was coupled in a Suzuki coupling reaction with 4-chlorobenzene boronic acid according to the procedure of step 2 example 1 to yield 69% of the title compound.

1H NMR (CDCl3) δ 1.30 (3H, t), 4.02 (2H, s), 4.22 (2H, q), 6.29 (1H, d), 6.99 (2H, d), 7.08 (1H, d), 7.20-7.30 (3H, m), 7.52 (1H, s) and 7.83 (1H, d).

Step 2: (E)-3-[5-Chloro-2-(4-chlorobenzyl)phenyl]-2-propenoic acid

The hydrolysis of the ester of Step 1 (1.14 g; 3.4 mmol) was done according to step 4 of example 1 to yield 860 mg (83%) of the title compound. The sodium salt was prepared with 1N NaOH.

1H NMR (CDCl3) δ 4.04 (2H, s), 6.30 (1H, d), 7.00 (2H, d), 7.10 (1H, d), 7.23 (2H, d), 7.29 (1H, d), 7.55 (1H, s) and 7.95 (1H, d).

LRMS calcd for M-1= 305.

EXAMPLE 25

(E)-3-{2-[(5-(PHENYLMETHOXY)INDOLYL)METHYL]-5-FLUOROPHENYL}-N-[(5-BROMO-2-METHOXYPHENYL)SULFONYL]-2-PROPENAMIDE (451)

Step 1: Ethyl (E)-3-(5-fluoro-2-methylphenyl)-2-propenoate

5-Fluoro-2-methylbenzaldehyde (40.58 g; 294 mmol) was converted to the ethyl cinnamate according to step 1 of example 1 to yield 40.81 g. of the title compound.

^{1}H NMR (acetone-d_6) δ 1.29 (3H, t), 2.40 (3H, s), 4.23 (2H, q), 6.49 (1H, d), 7.07 (1H, td), 7.29 (1H, dd), 7.46 (1H, dd) and 7.87 (1H, dd).

Step 2: Ethyl (E)-3-[2-(bromomethyl)-5-fluorophenyl]-2-propenoate

The ester of Step 1(40.80 g; 196 mmol) was converted to the benzylic bromide according to step 2 of example 1 to yield 24.17 g of the title compound.

^{1}H NMR (acetone-d_6) δ 1.30 (3H, t), 4.24 (2H, q), 4.81 (2H, s), 6.62 (1H, d), 7.18 (1H, td), 7.58 (2H, m) and 8.02 (1H, dd).

Step 3: Ethyl (E)-3-{2-[(5-(phenylmethoxy)indolyl)methyl]-5-fluorophenyl}-2-propenoate

The benzylic bromide of Step 2 (3.16 g; 11.0 mmol) was coupled with 5-(phenylmethoxy)indole according to the same procedure described in step 1 of example 2 to yield 2.27 g of the title compound.

^{1}H NMR (acetone-d_6) δ 1.27 (3H, t), 4.20 (2H, q), 5.11 (2H, s), 5.59 (2H, s), 6.43 (1H, dd), 6.52 (1H, d), 6.80 (1H, dd), 6.86 (1H, dd), 7.08 (1H, td), 7.19 (1H, d), 7.22 (1H, d), 7.31 (2H, m), 7.38 (2H, m), 7.50 (2H, m), 7.55 (1H, dd) and 8.01 (1H, dd).

Step 4: (E)-3-{2-[(5-(Phenylmethoxy)indolyl)methyl]-5-fluorophenyl}-2-propenoic acid (493)

The hydrolysis of the ester of Step 3 (2.27 g) was done according to step 4 of example 1 to yield 2.07 g of the title compound.

^{1}H NMR (acetone-d_6) δ 5.11 (2H, s), 5.62 (2H, s), 6.43 (1H, dd), 6.53 (1H, d), 6.75 (1H, dd), 6.86 (1H, dd), 7.08 (1H, td),), 7.19 (1H, d), 7.25 (1H, d), 7.31 (2H, m), 7.38 (2H, m), 7.50 (2H, m), 7.56 (1H, dd) and 8.04 (1H, dd). Elemental analysis calcd. for $C_{25}H_{20}FNO_3.2H_2O$: C, 68.64; H, 5.53; N, 3.20; Found: C, 68.16; H, 4.95; N, 3.06.

Step 5: (E)-3-{2-[(5-(Phenylmethoxy)indolyl)methyl]-5-fluorophenyl}-N-[(5-bromo-2-methoxyphenyl)sulfonyl]-2-propenamide

The acid of Step 5 (2.06; 5.13 mmol) was coupled with 5-bromo-2-methoxybenzenesulfonamide of example 10, step 5 according to step 5 of example 1 to yield 2.44 g of the title compound.

^{1}H NMR (acetone-d_6) δ 3.93 (3H, s), 5.10 (2H, s), 5.59 (2H, s), 6.39 (1H, dd), 6.73 (1H, dd), 6.78 (1H, d), 6.81 (1H, dd), 7.09 (1H, td),), 7.18 (1H, d), 7.24 (3H, m), 7.32 (1H, m), 7.39 (3H, m), 7.49 (2H, m), 7.82 (1H, dd), 8.01 (1H, dd) and 8.09 (1H, d). Elemental analysis calcd. for $C_{32}H_{26}BrFN_2O_5S_2$: C, 59.17; H, 4.03; N, 4.31; S, 4.94; Found: C, 59.07; H, 4.01; N, 4.34; S, 5.16.

EXAMPLE 26

(E)-3-[2-(BENZO[B]THIOPHEN-2-YLMETHYL)-5-FLUOROPHENYL]-N-[(5-BROMO-2-METHOXYPHENYL)SULFONYL]-2-PROPENAMIDE SODIUM SALT (452)

Step 1: Ethyl (E)-3-[2-(benzo[b]thiophen-2-ylmethyl)-5-fluorophenyl]-2-propenoate

The ester (901 mg, 3.14 mmol) of example 13, step 2 was coupled with benzo[b]thiophene-2-boronic acid (from Lancaster Chemical) in DME according to the same procedure described in step 3 of example 10 to yield 657 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 1.22 (3H, t), 4.16 (2H, q), 4.43 (2H, s), 6.50 (1H, d), 7.03 (1H, s), 7.15-7.35 (3H, m), 7.47 (1H, dd), 7.56 (1H, dd), 7.69 (1H, dd), 7.78 (1H, dd) and 8.00 (1H, dd).

Step 2: (E)-3-[2-(benzo[b]thiophen-2-ylmethyl)-5-fluorophenyl]-2-propenoic acid (539)

The hydrolysis of the ester of Step 1 (657 mg) was done according to step 4 of example 1 to yield 345 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 4.45 (2H, s), 6.51 (1H, d), 7.04 (1H, d), 7.2-7.3 (3H, m), 7.49 (1H, dd), 7.57 (1H, dd), 7.70 (1H, d), 7.80 (1H, m) and 8.01 (1H, dd). Elemental analysis calcd. for $C_{18}H_{13}FO_2S$: C, 69.21; H, 4.19; Found: C, 68.96; H, 4.15.

Step 3: (E)-3-[2-(Benzo[b]thiophen-2-ylmethyl)-5-fluorophenyl]-N-[(5-bromo-2-methoxyphenyl)sulfonyl]-2-propenamide

The previous acid (264 mg; 0.85 mmol) was coupled with 5-bromo-2-methoxybenzenesulfonamide of example 10, step 5 according to step 5 of example 1 to yield 287 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 3.83 (3H, s), 4.43 (2H, s), 6.77 (1H, d), 7.00 (1H, d), 7.13 (1H, d), 7.2-7.3 (3H, m), 7.41 (1H, dd), 7.49 (1H, dd), 7.65 (1H, dd), 7.78 (2H, m), 7.96 (1H, dd)HH and 8.05 (1H, d).

The acid was converted to the sodium salt with 1 equivalent of NaOH. Elemental analysis calcd. for $C_{25}H_{18}BrFNNaO_4S_2.H_2O$: C, 50.01; H, 3.36; N, 2.33; Found: C, 49.84; H, 3.22; N, 2.41.

EXAMPLE 27

N-(E)-[(5-BROMO-2-METHOXYPHENYL)SULFONYL]-3-(5-FLUORO-2-{[1-BENZYLINDOL-5-YL]METHYL}PHENYL)-2-PROPENAMIDE SODIUM SALT (453)

Step 1: Ethyl (E)-3-[5-fluoro-2-(indol-5-ylmethyl)phenyl]-2-propenoate

The ester (1.83 g, 6.37 mmol) of example 13, step 2 was coupled with 5-indolyl boronic acid and $NaHCO_3$ in DME according to the procedure described in step 3 of example 10 to yield 1.08 g of the title compound.

^1H NMR (acetone-d_6) δ 1.26 (3H, t), 4.17 (2H, q), 4.21 (2H, s), 6.37 (1H, m), 6.44 (1H, d), 6.94 (1H, dd), 7.14 (1H, td), 7.27-7.37 (4H, m), 7.51 (1H, dd), 8.05 (1H, dd) and 10.13 (1H, s).

Step 2: Ethyl (E)-3-(5-fluoro-2-{[1-benzylindol-5-yl]methyl}phenyl)-2-propenoate

The indole of Step 1 (621 mg; 1.92 mmol) was coupled with benzyl bromide according to the procedure described in step 1 of example 2 to yield 678 mg of the title compound.

^1H NMR (acetone-d_6) δ 1.26 (3H, t), 4.17 (4H, m), 5.32 (2H, s), 6.43 (2H, m), 6.95 (1H, dd), 7.1-7.4 (11H, m), 7.49 (1H, dd) and 8.08 (1H, dd).

Step 3: (E)-3-(5-Fluoro-2-{[1-benzylindol-5-yl]methyl}phenyl)-2-propenoic acid) (540)

The hydrolysis of the ester of Step 2 (678 mg) was done according to step 4 of example 1 to yield 276 mg of the title compound.

^1H NMR (acetone-d_6) δ 4.20 (2H, s), 5.38 (2H, s), 6.39 (1H, d), 6.45 (1H, d), 6.95 (1H, d), 7.1-7.3 (10H, m), 7.48 (1H, d) and 8.04 (1H, dd). Elemental analysis calcd. for $C_{25}H_{20}FNO_2$: C, 77.91; H, 5.23; N, 3.63; Found: C, 78.52; H, 5.46; N, 3.66.

Step 4: N-(E)-[(5-Bromo-2-methoxyphenyl)sulfonyl]-3-(5-fluoro-2-{[1-benzylindol-5-yl]methyl}phenyl)-2-propenamide

The acid of Step 3 (219 mg; 0.57 mmol) was coupled with 5-bromo-2-methoxybenzenesulfonamide of example 10, step 5 according to step 5 of example 1 to yield 149 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 3.82 (3H, s), 4.18 (2H, s), 5.38 (2H, s), 6.36 (1H, dd), 6.72 (1H, d), 6.90 (1H, dd), 7.1-7.4 (12H, m), 7.78 (1H, dd), 7.98 (1H, dd) and 8.05 (1H, d).

The acid was converted to the sodium salt with 1 equivalent of NaOH. Elemental analysis calcd. for $C_{32}H_{25}BrFN_2NaO_4S.1/2H_2O$: C, 57.84; H, 3.94; N, 4.22; Found: C, 57.61; H, 3.86; N, 4.16.

EXAMPLE 28

N-(E)-[(2,4-DIMETHYL(1,3-THIAZOL-5-YL))SULFONYL]-3-{3-[(5-CHLOROINDOLYL)METHYL](2-PYRIDYL)}-2-PROPENAMIDE (444)

Step 1: Ethyl (E)-3-(3-methyl-2-pyridyl)-2-propenoate

To a solution of 2-bromo-3-methylpyridine (10.36 g; 60.2 mmol) in 120 mL of THF at -100 °C was added dropwise a 1.6 M solution of n-BuLi (65.6 mmol). After 20 min of stirring at that temperature, 1-formylpiperidine (7.65 g) in 10 mL of THF was added and the solution was warmed to r.t.. After 30 min of stirring at r.t., triethyl phosphonoacetate (13.7 mL; 69.1 mmol) was added dropwise below 30 °C. After 1 h of stirring, the mixture was quenched with NH_4OAc (25%) and extracted with EtOAc. The solvent was removed and the crude oil was purified by silica gel chromatography (25% EtOAc in hexane) to yield 10.32 g of the title compound.

^1H NMR (acetone-d_6) δ 1.29 (3H, t), 2.46 (3H, s), 4.22 (2H, q), 6.99 (1H, d), 7.27 (1H, dd), 7.64 (1H, dt), 7.90 (1H, d) and 8.45 (1H, m).

Step 2: Ethyl (E)-3-[3-(bromomethyl)-2-pyridyl]-2-propenoate

The ester of Step 1 (5.93 g; 31.0 mmol) was converted in benzene to the benzylic bromide according to the procedure described in step 2 of example 1 to yield 1.83 g of the title compound.

^1H NMR (acetone-d_6) δ 1.30 (3H, t), 4.25 (2H, q), 4.88 (2H, s), 7.10 (1H, d), 7.41 (1H, dd), 7.91 (1H, dd), 8.03 (1H, d) and 8.60 (1H, dd).

Step 3: Ethyl (E)-3-{3-[(5-chloroindolyl)methyl]-2-pyridyl}-2-propenoate

The benzylic bromide of Step 2 (1.33 g; 4.91 mmol) was coupled with 5-chloroindole according to the procedure described in step 1 of example 2 to yield 1.22 g of the title compound.

^1H NMR (acetone-d_6) δ 1.28 (3H, t), 4.22 (2H, q), 5.78 (2H, s), 6.57 (1H, d), 6.94 (1H, d), 7.04 (1H, d), 7.11 (1H, dd), 7.27 (1H, dd), 7.43 (2H, m), 7.63 (1H, d), 7.99 (1H, d) and 8.53 (1H, d).

Step 4: (E)-3-{3-[(5-Chloroindolyl)methyl]-2-pyridyl}-2-propenoic acid (542)

The hydrolysis of the ester of Step 3 (283 mg) was done according to step 4 of example 1 to yield 291 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 5.81 (2H, s), 6.57 (1H, d), 6.88 (1H, d), 7.05 (1H, d), 7.11 (1H, dd), 7.26 (1H, dd), 7.43 (2H, m), 7.63 (1H, d), 8.02 (1H, d) and 8.54 (1H, d). Elemental analysis calcd. for $C_{17}H_{13}ClN_2O_2.1/4H_2O$: C, 64.36; H, 4.29; N, 8.83; Found: C, 64.63; H, 4.43; N, 8.65.

Step 5: N-(E)-[(2,4-Dimethyl(1,3-thiazol-5-yl))sulfonyl]-3-{3-[(5-chloroindolyl)methyl](2-pyridyl)}-2-propenamide

The acid of Step 4 (283 mg; 0.90 mmol) was coupled with 2,4-dimethyl-1,3-thiazole-5-sulfonamide (from Maybridge Chemical) according to step 5 of example 1 to yield 315 mg of the title compound.

^{1}H NMR (acetone-d_6) δ 2.64 (3H, s), 2.69 (3H, s), 5.81 (2H, s), 6.56 (1H, d), 6.84 (1H, d), 7.09 (1H, dd), 7.26 (1H, dd), 7.31 (1H, d), 7.41 (2H, m), 7.62 (1H, d), 8.05 (1H, d) and 8.51 (1H, d). Elemental analysis calcd. for $C_{22}H_{19}ClN_4O_3S_2$: C, 54.26; H, 3.93; N, 11.50; S, 13.17; Found: C, 54.69; H, 4.03; N, 11.18; S, 12.89.

EXAMPLE 29

N-{(E)-3-[5-CHLORO-2-(2-NAPHTHYLMETHYL)PHENYL]-2-PROPENOYL-2-METHOXYBENZENESULFONAMIDE (302)

The coupling reaction of the acid (3.00 g; 9.1 mmol) of Step 5 in Example 12 was done with 5-bromo-2-methoxybenzesulfonamide (2.56g; 9.6 mmol) according to Step 5 of Example 1 to yield 4.13g (79 %) of the title compound. The sodium salt was prepared with 1N NaOH.

^{1}H NMR (DMSO-d_6) d 3.76 (3H, s), 4.25 (2H, s), 6.52 (1H, d), 7.15 (1H, d), 7.26 (1H, d), 7.36 (1H, d), 7.41-7.52 (4H, m), 7.58 (1H, s), 7.69 (1H, m), 7.78 (1H, d), 7.82 (3H, m), 7.89 (1H, d) and 12.38 (1H, br s).

Elemental analysis:

Calcd. for $C_{27}H_{20}BrClNNaO_4S.H_2O$: C, 53.08; H, 3.64; N, 2.29;

Found: C, 53.25; H, 3.89; N, 2.91.

These intermediates were prepared according to the literature:

5-fluoro-2-methylbenzaldehyde:

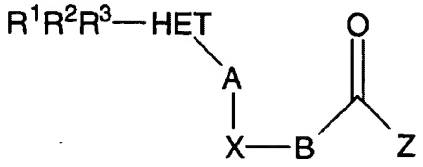
Servis, K. L.; Fang, K.-N. *J. Am. Chem. Soc.* **1968**, 90, 6712-6717.

5-indolyl boronic acid:

Yang, Y.; Martin, A. R. *Heterocycles* **1992**, 34, 1395-1398.

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



I

or a pharmaceutically acceptable salt, hydrate or ester thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$- or $-CR^7=CR^7$- , wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}$- ;

B represents $-(C(R^{18})_2)_p$-Y- $(C(R^{18})_2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}$- , p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, $-(C(R^4)2)_pSR^5$, $-(C(R^4)_2)_pOR^8$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, $-CO_2R^9$, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl,

or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})_{0-2}$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})_{0-3}$, $CH_2Ph(R^{11})_{0-3}$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R^{15} are independently lower alkyl, halogen, CF_3, OR^{16}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3, $HET(R^a)_{4-9}$, lower alkyl-$HET(R^a)_{4-9}$ or lower alkenyl-$HET(R^a)_{4-9}$;

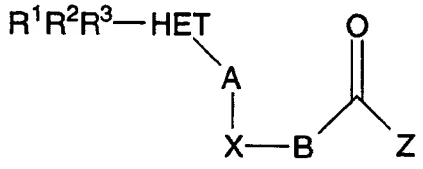
each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3 or $Ph(R^{13})_2$

and

each R^a is independently selected from the group consisting of:

H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, and CO_2C_{2-6}alkynyl, said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

2. A compound represented by formula I:



I

or a pharmaceutically acceptable salt, hydrate or ester thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$- or $-CR^7=CR^7$- , wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R17 as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}-$;

B represents $-(C(R^{18})_2)_p-Y-(C(R^{18})_2)_q-$

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}-$, p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, $-(C(R^4)2)_pSR^5$, $-(C(R^4)_2)_pOR^8$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, $-CO_2R^9$, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl, or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})_{0-2}$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})_{0-3}$, $CH_2Ph(R^{11})_{0-3}$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R15 are independently lower alkyl, halogen, CF_3, OR^{16}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn, CHF_2 or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3 , $HET^2(R^a)_{4-9}$, lower alkyl-$HET^2(R^a)_{4-9}$ or lower alkenyl-$HET^2(R^a)_{4-9}$, wherein HET^2 represents a member selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl;

each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 , CF_3 or $Ph(R^{13})_2$

and

each R^a is independently selected from the group consisting of:

H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, C(O) C_{2-6}alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, and CO_2C_{2-6}alkynyl,

said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}alkyl)_2$.

3. A compound in accordance with claim 1 wherein:
HET represents a member selected from the group consisting of: benzene, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, triazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, 1,3-methylenedioxobenzene and pyrrole.

4. A compound in accordance with claim 3 wherein:
HET is selected from the group consisting of: phenyl, biphenyl, naphthyl, indole, thiophene, benzofuran and quinoline.

5. A compound in accordance with claim 1 wherein:
A represents a one or two atom moiety and is selected from the group consisting of: S, S(O), SO_2, CH_2, -C(O)- , -OCH_2-, -CHOH- , -C(OH)(CH_3)- and -CH_2-O- .

6. A compound in accordance with claim 5 wherein:
A is selected from the group consisting of: : S, S(O), SO_2, CH_2 and -C(O)-.

7. A compound in accordance with claim 1 wherein:
X represents phenyl optionally substituted with R^{14} and R^{15}.

8. A compound in accordance with claim 7 wherein X represents phenyl and R^{14} and R^{15} are absent or represent halo.

9. A compound in accordance with claim 1 wherein:
B represents CH=CH or 1,2-cyclopropyl.

10. A compound in accordance with claim 9 wherein:
B represents CH=CH in the E-isomeric form.

11. A compound in accordance with claim 9 wherein:
Z is $NHSO_2R^{19}$.

12. A compound in accordance with claim 11 wherein:
Z is $NHSO_2R^{19}$ and R^{19} represents a member selected from the group consisting of: lower alkyl and $HET(R^a)_3$.

13. A compound in accordance with claim 12 wherein:
R19 represents $HET(R^a)_3$ and HET is selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl.

14. A compound in accordance with claim 12 wherein:
Z is $NHSO_2R^{19}$ and R^{19} represents benzene or thiophene, substituted with $(R^a)_3$.

15. A compound in accordance with claim 1 wherein:
Z represents OH.

16. A compound in accordance with claim 1 wherein:
HET represents a member selected from the group consisting of: phenyl, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole and pyrrole;
A represents a one or two atom moiety and is selected from the group consisting of: S, S(O), SO_2, CH_2, -C(O)- , $-OCH_2-$, -CHOH- , -C(OH)(CH_3)- and $-CH_2-O-$;
X represents phenyl optionally substituted with R^{14} and R^{15} ;
B is CH=CH;
Z is $NHSO_2R^{19}$ and
R^{19} represents a member selected from the group consisting of: lower alkyl and $HET(R^a)_3$.

17. A compound in accordance with claim 1 wherein:

HET represents a member selected from the group consisting of: phenyl, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole and pyrrole;

A represents a one or two atom moiety and is selected from the group consisting of: S, S(O), SO_2, CH_2, -C(O)- , $-OCH_2-$, -CHOH- , $-C(OH)(CH_3)-$ and $-CH_2-O-$;

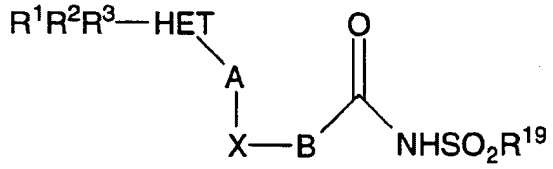
X represents phenyl optionally substituted with R^{14} and R^{15} ;

B is CH=CH;

Z is OH.

18. A compound represented in one of the following tables:

Table I



Ia

(Compounds 1-323 and 347-454)

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
1-naphthyl	CH_2	1,2-Ph	CH=CH	$Ph(F)_5$	1
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	$Ph(F)_5$	2
3-methylindol -1-yl	CH_2	1,2-Ph	CH=CH	2-thienyl	3
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	4
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	phenyl	5
3-methylindol -1-yl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	6

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	7
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	8
2-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	9
2,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	10
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	$Ph(F)_5$	11
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	12
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-thienyl	13
3,4-chloro fluoro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	14
1-naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	15
3,4-dichloro phenyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	16
4-methylthio phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	17
4-chlorophenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	18
2-naphthyl	S	1,2-Ph	CH=CH	2-thienyl	19
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	2-thienyl	20
2-naphthyl	S(O)	1,2-Ph	CH=CH	2-thienyl	21
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	phenyl	22
2-benzofuranyl	CH_2	1,2-Ph	CH=CH	2-thienyl	23
3,5-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	24
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	25
1-naphthyl	$S(O)_2$	1,2-Ph	CH=CH	2-thienyl	26
3-(1,2-(methylene dioxy)benzene)	CH_2	1,2-Ph	CH=CH	2-thienyl	27
2-naphthyl	O	1,2-Ph	CH=CH	2-thienyl	28
Rs-2-phenyl	CH_2	1,2-Ph	CH_2-O	2-thienyl	29
Rs-2-phenyl	CH_2	1,2-Ph	CH_2-CH_2	2-thienyl	30
2-naphthyl	$S(O)_2$	1,2-Ph	CH_2-O	2-thienyl	31
3-((2-(Qn)vinyl)) phenyl	CH_2	1,2-Ph	CH_2-O	2-thienyl	32
2-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	33
3-((2-(Qn)vinyl)) phenyl	SO	1,2-Ph	CH_2-O	2-thienyl	34
3-((2-(Qn)vinyl)) phenyl	-CHOH-	1,2-Ph	CH_2-O	2-thienyl	35

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-((2-(Qn)vinyl)) phenyl	$S(O)_2$	1,2-Ph	CH_2-O	phenyl	36
3-((2-(Qn)vinyl)) phenyl	O-CH_2	1,2-Ph	CH_2-O	2-thienyl	37
3-tolyl-D-3-phenyl	O-CH_2	1,2-Ph	CH_2-O	2-thienyl	38
3-((2-(Qn)vinyl)) phenyl	CH(OH)-CH_3-	1,2-Ph	CH_2-O	phenyl	39
3-((2-(Qn)vinyl)) phenyl	S	1,2-Ph	CH_2-O	2-thienyl	40
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	CH_2-O	phenyl	41
3-((2-(Qn)vinyl)) phenyl	C=O	1,2-Ph	CH_2-O	2-thienyl	42
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	$C(CH_3)_2$-O	2-thienyl	43
3-((2-(Qn)vinyl)) phenyl	O	1,2-Ph	CH_2-O	2-thienyl	44
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	45
2-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	46
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	47
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-fluoro phenyl	48
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-chloro phenyl	49
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-propyl phenyl	50
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dichloro thienyl	51
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	styryl	52
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	53
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	54
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-bromo phenyl	55
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	56
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	57
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	58

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	59
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-butyl-phenyl	60
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	butyl	61
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	62
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	63
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	64
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	65
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	66
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	67
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	68
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	69
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	70
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	71
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro-methyl)-hydroxy methyl)phenyl	72
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	73
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	74
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	75
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	cyclohexyl	76
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	cyclopentyl	77
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-morpholinYL	78
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-naphthyl	79
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	80
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	81
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-furanyl	82
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	83

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	84
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	85
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3-indolyl	86
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	87
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	88
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	89
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	90
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	91
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	92
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	93
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	94
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	95
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	96
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	97
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-butyl-phenyl	98
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3) phenyl	99
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)-hydroxy methyl)phenyl	100
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-bromophenyl	101
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	102
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	103
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	104
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	105
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	106

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	107
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	108
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	109
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-fluorophenyl	110
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	cyclohexyl	111
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	cyclopentyl	112
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-morpholinyl	113
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	butyl	114
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-chlorophenyl	115
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-propylphenyl	116
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-naphthyl	117
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-thiazolyl	118
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	1-imidazolyl	119
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	120
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	121
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	122
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-furanyl	123
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	124
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-pyridinyl	125
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-styryl	126
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-difluoro-phenyl	127
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3,5-dichloro-phenyl	128
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	129
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-indolyl	130
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-nitrophenyl	131
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	4-cyanophenyl	132
2-naphthyl	$S(O)_2$	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	133
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3)-phenyl	134
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	135
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	136

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	137
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-fluorophenyl	138
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-chlorophenyl	139
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-propylphenyl	140
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	141
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-styryl	142
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluoro phenyl	143
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	144
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-bromophenyl	145
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	146
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	147
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	148
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	149
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-butylphenyl	150
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	n-butyl	151
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	152
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-trifluoro methylphenyl	153
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	154
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	155
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	156
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	157

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	158
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	159
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	160
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	161
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)hydroxy methyl)phenyl	162
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	163
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl) ethyl)phenyl	164
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	165
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	cyclohexyl	166
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	cyclopentyl	167
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-morpholinyl	168
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-naphthyl	169
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	170
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	171
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-furanyl	172
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	173
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	174
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	175
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	3-indolyl	176
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	177
3-methylindol -1-yl	CH_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	178

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,5-di-(CF_3) phenyl	179
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-isopropyl phenyl	180
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,4-dichloro phenyl	181
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	182
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-fluorophenyl	183
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-chlorophenyl	184
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-propylphenyl	185
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dichloro-3-thienyl	186
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-styryl	187
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-chloro-4-fluorophenyl	188
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-methoxy phenyl	189
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-bromo phenyl	190
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dimethyl phenyl	191
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-nitro-4-chloro phenyl	192
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-carbomethoxy phenyl	193
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,4-difluoro phenyl	194
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-butylphenyl	195
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	n-butyl	196
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2,5-dimethoxy phenyl	197
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-trifluoromethyl phenyl	198
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3,5-difluoro phenyl	199
1-(3-methyl) indolyl	SO_2	1,2-Ph	1,2-c-propyl	3,5-dichloro phenyl	200

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((1-hydroxy-1-methyl)ethyl) phenyl	201
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(hydroxy methyl)phenyl	202
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(hydroxy methyl)phenyl	203
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(methyl sulfonyl)phenyl	204
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(methyl sulfonyl)phenyl	205
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(propyl sulfonyl)phenyl	206
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((bis-trifluoro methyl)hydroxy methyl)phenyl	207
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-(benzyloxy) phenyl	208
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-((1-methoxy-1-methyl)ethyl)-phenyl	209
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-dimethyl aminophenyl	210
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	cyclohexyl	211
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	cyclopentyl	212
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-morpholinyl	213
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-naphthyl	214
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-thiazolyl	215
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	1-imidazolyl	216
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-furanyl	217
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-(2-chloro)-furanyl	218
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-pyridinyl	219
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-(4-chloro) pyridinyl	220

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	3-indolyl	221
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-nitrophenyl	222
3-methylindol -1-yl	SO_2	1,2-Ph	1,2-c-propyl	4-cyanophenyl	223
2-naphthyl	CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	224
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-isopropyl phenyl	225
2-naphthyl	CH_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	226
2-naphthyl	CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	227
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-chlorophenyl	228
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-fluorophenyl	229
2-naphthyl	CH_2	1,2-Ph	CH=CH	2,5-dichloro-3-thienyl	230
2-naphthyl	CH_2	1,2-Ph	CH=CH	3-chloro-4-fluoro phenyl	231
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-methoxy phenyl	232
2-naphthyl	CH_2	1,2-Ph	CH=CH	butyl	233
2-naphthyl	CH_2	1,2-Ph	CH=CH	3-trifluoro methylphenyl	234
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-((1-hydroxy-1-methyl)ethyl) phenyl	235
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-(methyl sufonyl)phenyl	236
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-(benzyloxy) phenyl	237
2-naphthyl	CH_2	1,2-Ph	CH=CH	cyclohexyl	238
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-morpholinyl	239
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-thiazolyl	240
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-furanyl	241
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-pyridinyl	242
2-naphthyl	CH_2	1,2-Ph	CH=CH	4-cyanophenyl	243
2-naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	244
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-isopropyl phenyl	245
2-naphthyl	SO_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	246

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	SO_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	247
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-chlorophenyl	248
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-fluorophenyl	249
2-naphthyl	SO_2	1,2-Ph	CH=CH	2,5-dichloro-3-thienyl	250
2-naphthyl	SO_2	1,2-Ph	CH=CH	3-chloro-4-fluorophenyl	251
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-methoxy phenyl	252
2-naphthyl	SO_2	1,2-Ph	CH=CH	butyl	253
2-naphthyl	SO_2	1,2-Ph	CH=CH	3-trifluoro methylphenyl	254
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-((1-hydroxy-1-methyl)ethyl) phenyl	255
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-(methyl sufonyl)phenyl	256
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-(benzyloxy) phenyl	257
2-naphthyl	SO_2	1,2-Ph	CH=CH	cyclohexyl	258
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-morpholinyl	259
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-thiazolyl	260
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-furanyl	261
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-pyridinyl	262
2-naphthyl	SO_2	1,2-Ph	CH=CH	4-cyanophenyl	263
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	264
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	4-isopropyl phenyl	265
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	2,3-dichloro phenyl	266
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	3,4-difluoro phenyl	267
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	268
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	4-isopropyl phenyl	269
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	2,3-dichloro phenyl	270
2-naphthyl	O-CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	271
2-naphthyl	S	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	272

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	S	1,2-Ph	CH=CH	4-isopropyl phenyl	273
2-naphthyl	S	1,2-Ph	CH=CH	2,3-dichloro phenyl	274
2-naphthyl	S	1,2-Ph	CH=CH	3,4-difluoro phenyl	275
2-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	276
2-(6-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-thienyl	277
2-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	2-thienyl	278
2-(6-benzyloxy) naphthyl	S	1,2-Ph	1,2-c-propyl	2-thienyl	279
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	280
2-(5-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-thienyl	281
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	2-thienyl	282
2-(5-benzyloxy) naphthyl	S	1,2-Ph	1,2-c-propyl	2-thienyl	283
2-(6-(4-trifluoro methyl)benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	284
2-(6-(4-trifluoro methyl)benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	285
2-(6-(4-trifluoro methyl)benzyl oxy))naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	286
2-(6-(4-trifluoro methyl)benzyl oxy))naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	287
1-(6-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	288
1-(6-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	289
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	290
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	2-thienyl	291

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(6-(4-fluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-thienyl	292
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-thienyl	293
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	294
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	3,4-difluoro phenyl	295
2-(6-(4-fluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	296
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	297
2-(6-(3,4-difluoro benzyloxy)) naphthyl	SO_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	298
2-(6-(3,4-difluoro benzyloxy)) naphthyl	CH_2	1,2-Ph	CH=CH	3,5-di-(CF_3) phenyl	299
2-(7-benzyloxy) naphthyl	SO_2	1,2-Ph	1,2-c-propyl	3,4-difluoro phenyl	300
2-naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	301
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	302
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	303
2-naphthyl	SO	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	304
2-naphthyl	SO_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	305
2-naphthyl	O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	306
2-(5-benzyloxy) naphthyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	307
2-(5-benzyloxy) naphthyl	SO_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	308
2-(5-benzyloxy) naphthyl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	309
2-naphthyl	CH_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	310
1,2-Ph	SO_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	311

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	S	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	312
2-naphthyl	CH_2-O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	313
2-naphthyl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	314
3-methyl indol-1-yl	SO_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	315
3-methyl indol-1-yl	S	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	316
3-methyl indol-1-yl	CH_2-O	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	317
3-methyl indol-1-yl	S	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	318
3-methyl indol-1-yl	O-CH_2	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	319
3-methyl indol-1-yl	SO	1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	320
3-methyl indol-1-yl	CH_2-O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	321
3-methyl indol-1-yl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	322
3-methyl indol-1-yl	SO_2	4-Cl-1,2-Ph	1,2-c-propyl	2-methoxy-5-bromophenyl	323
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	347
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	348
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	349
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	350
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	351
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	352
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	353
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	354
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	355
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	356

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-naphthyl	CH_2	4,5-Cl_2-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	357
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	358
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	359
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	360
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	361
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	362
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	363
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	364
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	365
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-trifluoro methoxy-5-chlorophenyl	366
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-trifluoro methoxy-5-chlorophenyl	367
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	368
2-(7-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	369
2-(7-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	370
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	371
2-(7-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	372
2-(7-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	373
2-(7-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	374

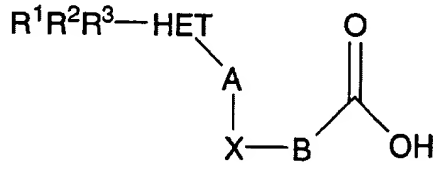
$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(7-fluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	375
2-(6-fluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	376
2-(6-fluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	377
2-(6-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	378
2-(6-fluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	379
2-(6-fluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	380
2-(6-fluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	381
2-(7-chloro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	382
2-(7-chloro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	383
2-(7-chloro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	384
2-(7-chloro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	385
2-(7-chloro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	386
2-(7-chloro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	387
2-(7-chloro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	388
2-(6,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	389
2-(6,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	390
2-(6,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	391
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	392
2-(6,7-difluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-thienyl	393
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-thienyl	394
2-(6,7-difluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-thienyl	395
2-(6,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	396

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
2-(6,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	397
2-(6,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	398
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	399
2-(6,7-difluoro) naphthyl	CH_2	6-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	400
2-(6,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	401
2-(6,7-difluoro) naphthyl	CH_2	3-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	402
2-(5,7-difluoro) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	403
2-(5,7-difluoro) naphthyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	404
2-(5,7-difluoro) naphthyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	405
2-(5,7-difluoro) naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	406
2-(6-fluoro) quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	407
2-(6-fluoro) quinolinyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	408
2-(6-fluoro) quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	409
2-(6-fluoro) quinolinyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	410
2-(6-fluoro) quinolinyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	411
2-(6-fluoro) quinolinyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	412
2-(5,7-difluoro)-quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	413
2-(5,7-difluoro)-quinolinyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	414
2-(5,7-difluoro)-quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	415
2-(5,7-difluoro)-quinolinyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	416
2-(5,7-difluoro)-quinolinyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	417
2-(5,7-difluoro)-quinolinyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	418

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
3,4-dichloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	419
3,4-dichloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	420
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	421
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	422
3,4-dichloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	423
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	424
3,4-dichloro phenyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	425
4-chloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	426
4-chloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	427
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	428
4-chloro phenyl	CH_2	1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	429
4-chloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	430
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	2-methoxy-5-bromophenyl	431
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	432
3,4-dichloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	433
3,4-dichloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	434
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	435
3,4-dichloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	436
3,4-dichloro phenyl	O	4-Cl-1,2-Ph	CH=CH	2-thienyl	437
3,4-dichloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	438
3,4-dichloro phenyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-thienyl	439
4-chloro phenyl	SO_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	440

$R^1R^2R^3$-Het	A	X	B	R^{19}	Cpd
4-chloro phenyl	S	4-Cl-1,2-Ph	CH=CH	2-thienyl	441
4-chloro phenyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-thienyl	442
4-chloro phenyl	CH_2	1,2-Ph	CH=CH	2-thienyl	443
1-(5-chloro) indolyl	CH_2	3,2-Pyr	CH=CH	2,4-(Me)2-thiazol-5-yl	444
1-(5-chloro) indolyl	CH_2	3,2-Pyr	CH=CH	2-thienyl	445
1-(6-(4-chloro) phenyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	3-chloro-4-fluorophenyl	446
2-(6-difluoro methoxy) naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	447
2-naphthyl	CH_2	4-MeO-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	448
2-naphthyl	CH_2	5-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	449
2-(6-chloro naphthyl)	CH_2	4-Cl-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	450
1-(5-phenyl methoxy) indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	451
2-(benzo[b] thiophenyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	452
5-(1-benzyl) indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	453
1-(6-(4-chloro) phenyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	2-methoxy-5-bromophenyl	454

Table II



I-b

(Compounds 324-346 and 455-542)

$R^1R^2R^3$-Het	A	X	B	Cpd
2-naphthyl	$S(O)_2$	1,2-phenyl	CH=CH	324
2-naphthyl	S	1,2-phenyl	CH=CH	325
4-methylthiophenyl	CH_2	1,2-phenyl	CH=CH	326
3-methylindol-1-yl	CH_2	1,2-phenyl	CH=CH	327
3-chloro-4-fluorophenyl	CH_2	1,2-phenyl	CH=CH	328
4-chlorophenyl	CH_2	1,2-phenyl	CH=CH	329
2-naphthyl	CH_2	1,2-phenyl	CH=CH	330
2-naphthyl	$S(O)_2$	1,2-phenyl	1,2-c-propyl	331
2-naphthyl	$S(O)_2$	1,2-phenyl	CH_2-CH_2	332
2-naphthyl	S	1,2-phenyl	CH=CH	333
3,4-dichlorophenyl	$S(O)_2$	1,2-phenyl	CH_2-CH_2	334
3,4-dichlorophenyl	CH_2	1,2-phenyl	CH=CH	335
2-(6-benzyloxy)naphthyl	CH_2	1,2-phenyl	CH=CH	336
2-(6-benzyloxy)naphthyl	CH_2	1,2-phenyl	1,2-c-propyl	337
2-(6-benzyloxy)naphthyl	SO_2	1,2-phenyl	1,2-c-propyl	338
2-(6-benzyloxy)naphthyl	CH_2-O	1,2-phenyl	1,2-c-propyl	339
2-(6-benzyloxy)naphthyl	O-CH_2	1,2-phenyl	1,2-c-propyl	340
2-(6-benzyloxy)naphthyl	SO_2	1,2-phenyl	CH=CH	341
2-(6-benzyloxy)naphthyl	CH_2-O	1,2-phenyl	CH=CH	342
2-(6-benzyloxy)naphthyl	O-CH_2	1,2-phenyl	CH=CH	343
2-(6-benzyloxy)naphthyl	S	1,2-phenyl	CH=CH	344
2-(7-benzyloxy)naphthyl	SO_2	1,2-phenyl	CH=CH	345
2-(6-(4-trifluoromethyl) benzyloxy))naphthyl	CH_2	1,2-phenyl	CH=CH	346
2-(6-fluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	455
2-(6-fluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	456
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	457
2-(6-fluoro)naphthyl	CH_2	1,2-Ph	CH=CH	458
2-(6-fluoro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	459
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	460
2-(7-fluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	461
2-(7-fluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	462
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	463
2-(7-fluoro)naphthyl	CH_2	1,2--Ph	CH=CH	464
2-(7-fluoro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	465
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	466
2-(6-chloro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	467
2-(6-chloro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	468
2-(6-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	469
2-(6-chloro)naphthyl	CH_2	1,2-Ph	CH=CH	470
2-(6-chloro)naphthyl	O	4-Cl-1,2-Ph	CH=CH	471

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(6-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	472
2-(7-chloro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	473
2-(7-chloro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	474
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	475
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	476
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	477
2-(7-chloro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	478
2-(6,7-difluoro)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	479
2-(6,7-difluoro)naphthyl	S	4-Cl-1,2-Ph	CH=CH	480
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	481
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	482
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	483
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	484
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	485
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	486
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	487
2-(6,7-difluoro)naphthyl	CH_2	1,2-Ph	CH=CH	488
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	489
2-(6,7-difluoro)naphthyl	CH_2	4-Cl-1,2-Ph	1,2-c-Pr	490
3-methyl-5-fluoro indol-1-yl	SO_2	4-Cl-1,2-Ph	CH=CH	491
3-methyl-5-fluoro indol-1-yl	S	4-Cl-1,2-Ph	CH=CH	492
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	493
3-methyl-5-fluoro indol-1-yl	CH_2	1,2-Ph	CH=CH	494
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	495
3-methyl-5-fluoro indol-1-yl	CH_2	4-Cl-1,2-Ph	CH=CH	496
2-(6-fluoro)quinolinyl	SO_2	4-Cl-1,2-Ph	CH=CH	497
2-(6-fluoro)quinolinyl	S	4-Cl-1,2-Ph	CH=CH	498
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	499
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	500
2-(6-fluoro)quinolinyl	O	4-Cl-1,2-Ph	CH=CH	501
2-(6-fluoro)quinolinyl	CH_2	4-Cl-1,2-Ph	CH=CH	502
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	503
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	504
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	505

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	506
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	507
2-(6-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	508
2-(7-difluoromethoxy)-naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	509
2-(7-difluoromethoxy)-naphthyl	S	4-Cl-1,2-Ph	CH=CH	510
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	511
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	512
2-(7-difluoromethoxy)-aphthyl	O	4-Cl-1,2-Ph	CH=CH	513
2-(7-difluoromethoxy)-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	514
2-(6-methoxy)naphthyl	SO_2	4-Cl-1,2-Ph	CH=CH	515
2-(6-methoxy)naphthyl	S	4-Cl-1,2-Ph	CH=CH	516
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	517
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	518
2-(6-methoxy)naphthyl	O	4-Cl-1,2-Ph	CH=CH	519
2-(6-methoxy)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	520
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	521
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	522
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	523
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	524
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	525
2-(6-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	526
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	527
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	528
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	529
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	530
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	531
2-(7-fluoro)naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	532
2-naphthyl	CH_2	4,5-Cl_2-1,2-Ph	CH=CH	533
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	534
3,4-dichlorophenyl	CH_2	4-Cl-1,2-Ph	CH=CH	535
2-naphthyl	CH_2	4-Cl-1,2-Ph	CH=CH	536
4-chlorophenyl	CH_2	4-Cl-1,2-Ph	CH=CH	537
1-(5-phenylmethoxy) indolyl	CH_2	4-F-1,2-Ph	CH=CH	538

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(benzo[b]thiophenyl)	CH_2	4-F-1,2-Ph	CH=CH	539
5-(1-benzyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	540
1-(6-(4-chloro)phenyl) indolyl	CH_2	4-F-1,2-Ph	CH=CH	541
1-(5-chloro)indolyl	CH_2	3,2-Pyr	CH=CH	542

wherein D= $-O(CH_2)_3-O$, Qn= 7-chloroquinolin-2-yl, 1,2-Ph = 1,2-benzenediyl, R^s = $-CH_2SCH_2CH_2Ph$, Pyr = pyridinediyl, c-pr = cyclopropyl and Bn = benzyl.

19. A pharmaceutical composition which is comprised of a compound in accordance with any one of claims 1 to 18 in combination with a pharmaceutically acceptable carrier.

20. A method of treating or preventing a prostaglandin mediated disease which is comprised of administering to a mammalian patient in need of such treatment a compound in accordance with claim 1 in an amount which is effective for treating or preventing a prostaglandin mediated disease.

21. A method in accordance with claim 19 wherein the prostaglandin mediated disease is selected from the group consisting of:

pain, fever or inflammation associated with rheumatic fever, influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases;

cellular neoplastic transformations or metastic tumor growth;

diabetic retinopathy, tumor angiogenesis;

prostanoid-induced smooth muscle contraction associated with dysmenorrhea, premature labor, asthma or eosinophil related disorders;

Alzheimer's disease;

glaucoma;

bone loss;

osteoporosis;

promotion of bone formation;

Paget's disease;

cytoprotection in peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or other gastrointestinal lesions; GI bleeding and patients undergoing chemotherapy;

coagulation disorders selected from hypoprothrombinemia, haemophilia and other bleeding problems;

kidney disease;

thrombosis;

occlusive vascular disease;

presurgery;

and anti-coagulation.

22. A method in accordance with claim 20 wherein the prostaglandin mediated disease is selected from the group consisting of: pain, fever or inflammation.

23. A method in accordance with claim 20 wherein the prostaglandin mediated disease is dysmenorrhea.

24. A method in accordance with claim 20, wherein the compound is co-administered with other agents or ingredients.

25. A method in accordance with claim 24 wherein the compound I is co-administered with another agent or ingredient selected from the group consisting of: an analgesic selected from acetaminophen, phenacetin, aspirin, a narcotic;

a COX-2 selective NSAID and a conventional NSAID;

caffeine;

an H_2-antagonist;

aluminum or magnesium hydroxide;

simethicone;

a decongestant selected from phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine;

an antiitussive selected from codeine, hydrocodone, caramiphen, carbetapentane and dextramethorphan;

another prostaglandin ligand selected from misoprostol, enprostil, rioprostil, ornoprostol and rosaprostol; a diuretic; and

a sedating or non-sedating antihistamine.

26. Use of a compound, salt, hydrate or ester as defined in any one of claims 1 to 18 in the manufacture of a medicament for treatment or prevention of a prostaglandin mediated disease.

27. A compound, salt, hydrate or ester as defined in any one of claims 1 to 18 for use in the treatment or prevention of a prostaglandin mediated disease.

28. A prostaglandin antagonist pharmaceutical composition comprising an acceptable prostaglandin antagonistic amount of a compound, salt, hydrate or ester as defined in any one of claims 1 to 18, in association with a pharmaceutically acceptable carrier.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 57/42, 59/68, 59/84, 311/51,
C07D 209/10, 307/64, 307/79

A3

(11) International Publication Number: WO 99/47497

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/CA99/00212

(22) International Filing Date: 12 March 1999 (12.03.99)

(30) Priority Data:

60/077,990	13 March 1998 (13.03.98)	US
9815856.1	21 July 1998 (21.07.98)	GB

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(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

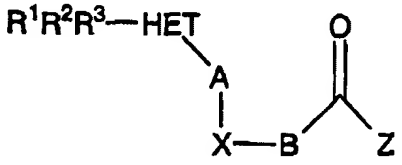
Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
28 October 1999 (28.10.99)

(54) Title: CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(I)

(57) Abstract

Compounds of formula (I), as well as pharmaceutically acceptable salts, hydrates and esters thereof, are disclosed. The compounds are useful for treating or preventing prostaglandin mediated diseases. Pharmaceutical compositions containing such compounds and methods of treatment are also included.

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